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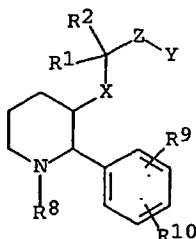
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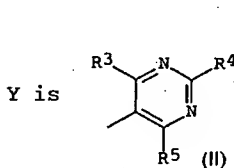
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(54) Title: PIPERIDYL DERIVATIVES

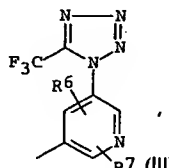


(I)

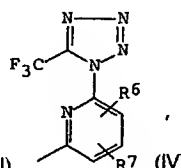
-X- is -NH or -O-,



(II)

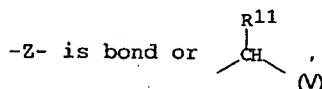


(III)



(IV)

etc., and



(V)

(57) Abstract: A compound of the formula (I): wherein R¹, R², R⁸, R⁹ and R¹⁰ are each as defined in the description, and -X- is -NH or -O-, Y is (II), (III), (IV), etc., and -Z- is bond or (V) in which R³, R⁴, R⁵, R⁶, R⁷, and R¹¹ are each as defined in the description, or a salt thereof. The object compound of the present invention has pharmacological activities such as Tachykinin antagonism, and is useful for manufacture of a medicament for treating or preventing Tachykinin-mediated diseases.



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GW, ML, MR, NE, SN, TD, TG).

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DESCRIPTION

PIPERIDYL DERIVATIVES

5 TECHNICAL FIELD

The present invention relates to new piperidyl derivatives and a salt thereof.

More particularly, it relates to new piperidyl derivatives and a salt thereof which have pharmacological
10 activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the like, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a use of the same as a medicament.

15 Accordingly, one object of the present invention is to provide new and useful piperidyl derivatives and a salt thereof which have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the
20 like.

Another object of the present invention is to provide a process for the preparation of said piperidyl derivatives and a salt thereof.

A further object of the present invention is to provide
25 a pharmaceutical composition comprising, as an active ingredient, said piperidyl derivatives and a pharmaceutically acceptable salt thereof.

Still further object of the present invention is to provide a use of said piperidyl derivatives or a
30 pharmaceutically acceptable salt thereof as Tachykinin antagonist, especially Substance P antagonist, Neurokinin A antagonist or Neurokinin B antagonist, useful for treating or preventing Tachykinin-mediated diseases, for example, respiratory diseases such as asthma, bronchitis, rhinitis,
35 cough, expectorations, and the like; ophthalmic diseases such

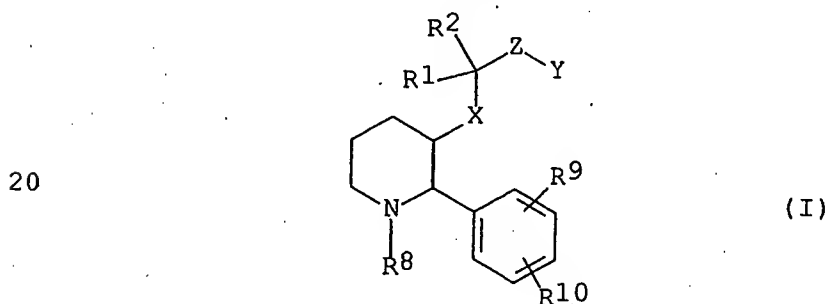
as conjunctivitis, vernal conjunctivitis, and the like;
 cutaneous diseases such as contact dermatitis, atopic
 dermatitis, urticaria, and other eczematoid dermatitis, and
 the like; inflammatory diseases such as rheumatoid arthritis,
 5 osteoarthritis, and the like; pains or aches (e.g., migraine,
 headache, toothache, cancerous pain, back pain, etc.); and
 the like in human being or animals.

BACKGROUND ART

10 Some piperidyl derivatives have been known as described
 in, for example, WO 93/01170, WO 95/08549 and WO 96/29326.

DISCLOSURE OF INVENTION

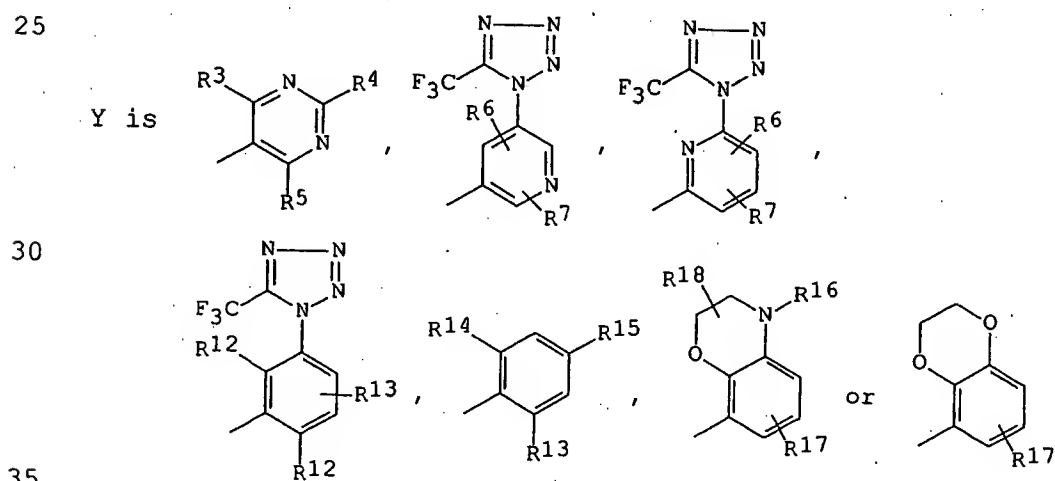
The object compound of the present invention can be
 15 represented by the following general formula (I):



wherein

-X- is -NH or -O-;

Y is



(in which R³, R⁴ and R⁵ are independently hydrogen,
lower alkyl, mono(or di or
tri)halo(lower)alkyl, cyclo(lower)alkyl,
lower alkoxy, mono(or di or
tri)halo(lower)alkoxy,
cyclo(lower)alkyloxy or
tetrahydrofranyloxy;

R⁶, R⁷ and R¹⁷ are independently hydrogen or
lower alkoxy;

R¹² is lower alkoxy;

R¹³ is hydrogen or lower alkoxy;

R¹⁴ is hydrogen or lower alkoxy(lower)alkoxy
or carbamoyl(lower)alkoxy;

R¹⁵ is hydrogen or isopropoxy;

R¹⁶ is hydrogen or mono(or di or
tri)halo(lower)alkyl; and

R¹⁸ is hydrogen or oxo);

-Z- is bond or

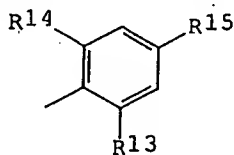


(in which R¹¹ is hydrogen or lower alkyl),

R¹ and R² are independently hydrogen or lower alkyl, or join
together to form oxo;

R⁸ is hydrogen, (5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-
yl)methyl or an amino protective group; and

R⁹ and R¹⁰ are independently hydrogen, halogen, lower alkyl
or lower alkoxy, and



provided that when Y is

(in which

R¹³, R¹⁴ and R¹⁵ are each as defined
above, then

-Z- is



(in which R¹¹ is as defined
above),

and a salt thereof.

It is to be noted that the object compound (I) may include one or more stereoisomers due to asymmetric carbon atom(s) and double bond, and all of such isomers and a mixture thereof are included within the scope of the present invention.

It is further to be noted that isomerization or rearrangement of the object compound (I) may occur due to the effect of the light, acid, base or the like, and the compound obtained as the result of said isomerization or rearrangement is also included within the scope of the present invention.

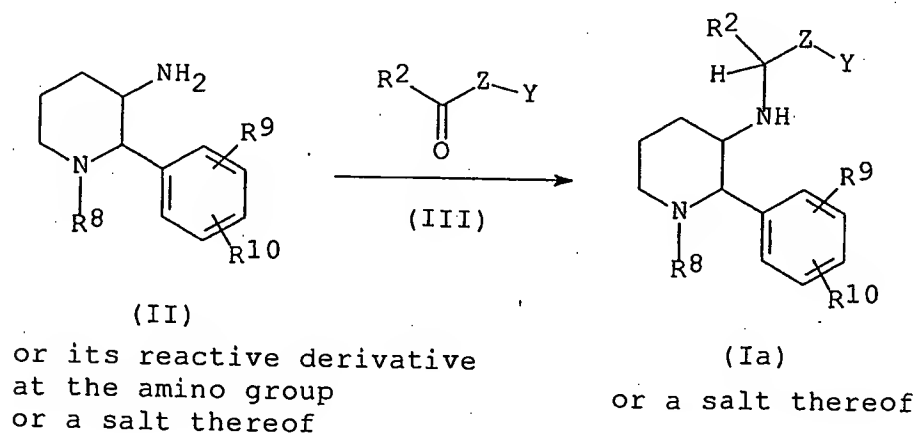
It is also to be noted that the solvating form of the compound (I) (e.g. hydrate, etc.) and any form of the crystal of the compound (I) are included within the scope of the present invention.

According to the present invention, the object compound (I) or a salt thereof can be prepared by processes which are illustrated in the following schemes.

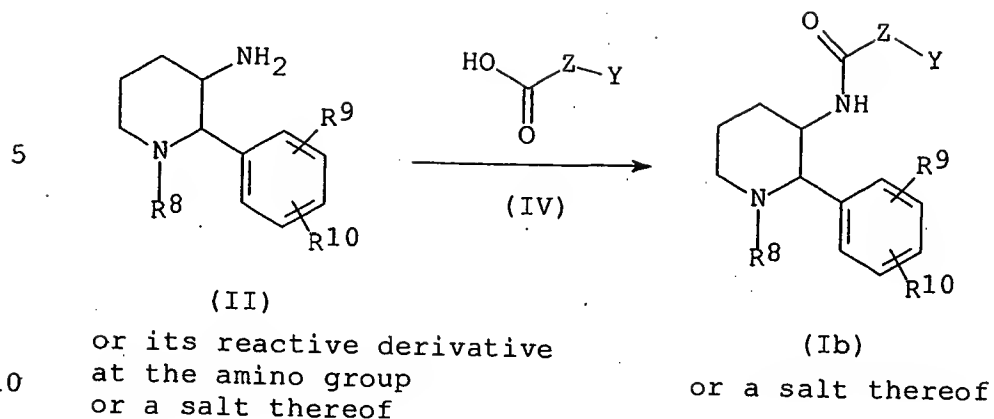
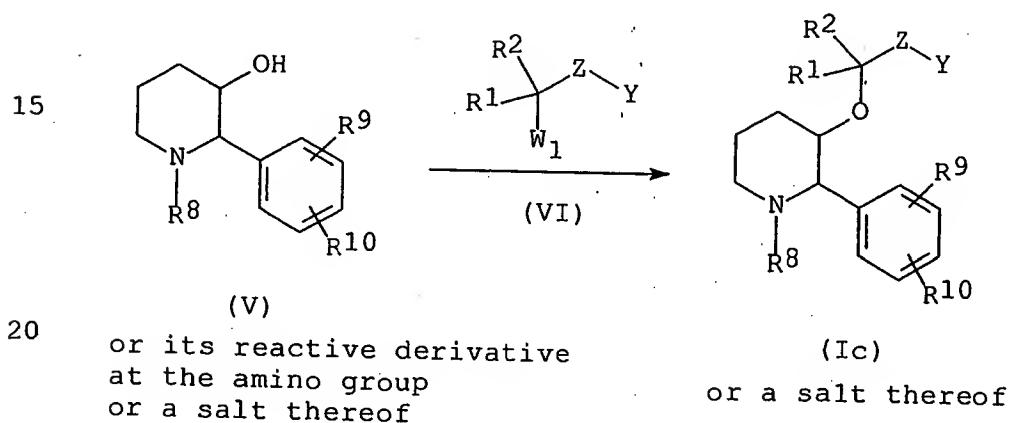
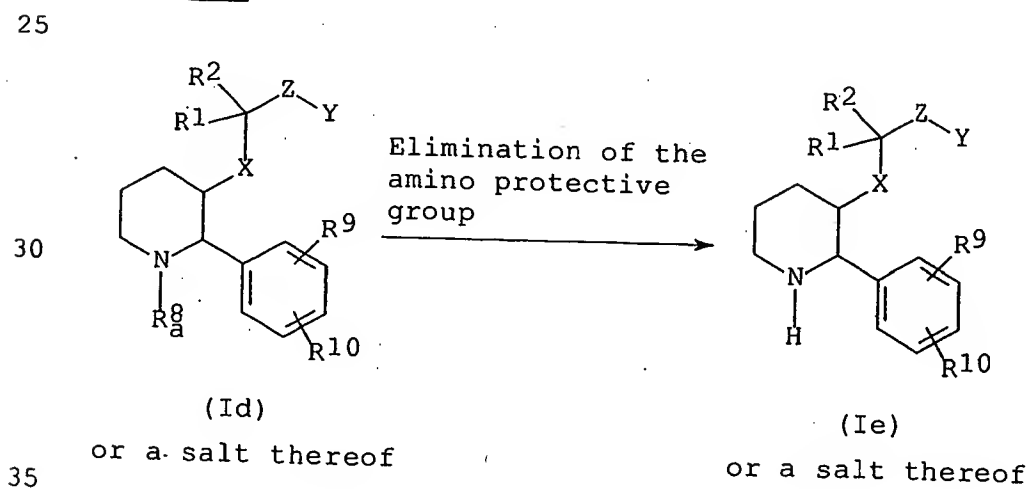
Process 1

25

30



35

Process 2Process 3Process 4

wherein

X, Y, Z, R¹, R², R⁸, R⁹ and R¹⁰ are each as defined above, R_a⁸ is an amino protective group, and W₁ is a leaving group.

5

As to the starting compounds (II), (III), (IV), (V) and (VI), some of them are novel and can be prepared by the procedures described in the Preparations and Examples mentioned later or similar manners thereto.

10 Suitable salts of the starting and object compounds are conventional non-toxic and pharmaceutically acceptable salt and include an acid addition salt such as an organic acid salt (e.g. acetate, trifluoroacetate, fumarate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, 15 toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, etc.), or a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), or a metal salt such as an alkali metal salt (e.g. sodium salt, 20 potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), or the like.

25

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention intends to include within the scope thereof are explained in detail as 30 follows.

The term "lower" is intended to mean 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise indicated.

Suitable "halogen" may include fluorine, chlorine, 35 bromine and iodine.

Suitable "lower alkyl" and "lower alkyl" moiety in the term of "mono(or di or tri)halo(lower)alkyl" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, 5 hexyl and the like, in which the preferred one is C₁-C₄ alkyl and the most preferred one is methyl, ethyl, propyl or tert-butyl.

Suitable "mono(or di or tri)halo(lower)alkyl" may be fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, 10 dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, 1 or 2-fluoroethyl, 1 or 2-bromoethyl, 1 or 2-chloroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, and the like, in which the preferred one may be trifluoromethyl.

15 Suitable "cyclo(lower)alkyl" and "cyclo(lower)alkyl" moiety in the term of "cyclo(lower)alkyloxy" may include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like, in which the preferred one is cyclo(C₃-C₆)alkyl and the most preferred one is cyclopropyl 20 or cyclobutyl.

Suitable "lower alkoxy" and "lower alkoxy" moiety in the term of "mono(or di or tri)halo(lower)alkoxy" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy, hexyloxy 25 and the like, in which the preferred one is C₁-C₄ alkoxy and the most preferred one is methoxy, ethoxy, isopropoxy or tert-butoxy.

Suitable "mono(or di or tri)halo(lower)alkoxy" may include chloromethoxy, dichloromethoxy, trichloromethoxy, 30 bromomethoxy, dibromomethoxy, tribromomethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1 or 2-chloroethoxy, 1 or 2-bromoethoxy, 1 or 2-fluoroethoxy, 1,1-difluoroethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, and the like, in which the preferred one may be 2,2,2-trifluoroethoxy.

35 Suitable "leaving group" may include lower alkoxy (e.g.

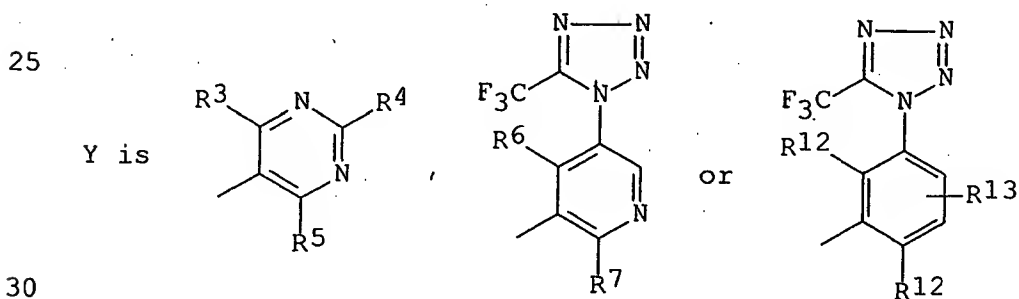
methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentoxy, etc.), aryloxy (e.g., phenoxy, naphthoxy, etc.), an acid residue or the like.

Suitable "acid residue" may be halogen (e.g., chlorine, bromine, iodine, etc.), sulfonyloxy (e.g., methanesulfonyloxy, phenylsulfonyloxy, mesitylenesulfonyloxy, toluenesulfonyloxy, etc.) or the like.

Suitable example of "amino protective group" moiety may be common amino protective group such as acyl, for example, substituted or unsubstituted lower alkanoyl [e.g. formyl, acetyl, propionyl, trifluoroacetyl, etc.], phthaloyl, lower alkoxy-carbonyl [e.g. tert-butoxycarbonyl, tert-amyl-oxycarbonyl, etc.], substituted or unsubstituted aralkyloxy-carbonyl [e.g. benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.], substituted or unsubstituted arenesulfonyl [e.g. benzenesulfonyl, tosyl, etc.], nitrophenylsulfenyl, ar(lower)alkyl [e.g. trityl, benzyl, etc.], and the like, in which preferable one is tert-butoxycarbonyl.

Preferred embodiments of the object compound (I) are as follows:

-X- is -NH or -O-;



(in which R^3 , R^4 and R^5 are independently hydrogen, lower alkyl, cyclo(lower)alkyl, lower alkoxy or cyclo(lower)alkoxy;

R^6 and R^7 are independently hydrogen or lower alkoxy;

R^{12} is lower alkoxy; and
 R^{13} is hydrogen or lower alkoxy);

-Z- is bond;

R^1 and R^2 are independently hydrogen or lower alkyl;

5 R^8 is hydrogen; and

R^9 and R^{10} are each hydrogen.

The Processes 1, 2, 3 and 4 for preparing the object compound (I) of the present invention are explained in
10 detail in the following.

Process 1

The object compound (Ia) or a salt thereof can be prepared by reacting the compound (II) or its reactive
15 derivative at the amino group or a salt thereof with the compound (III).

Suitable reactive derivative at the amino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the
20 compound (II) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by
25 reaction of the compound (II) with phosphorus trichloride or phosgene and the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g. methanol, ethanol, etc.), acetone, dioxane, acetonitrile, chloroform, methylene
30 chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction, or the mixture thereof.

The reaction may also be carried out in the presence of
35 a reductive reagent such as hydrides (e.g. hydrogen iodide,

hydrogen sulfide, lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, etc.), or the like.

The reaction temperature is not critical, and the
5 reaction is usually carried out under cooling to heating.

Process 2

The object compound (Ib) or a salt thereof can be prepared by reacting the compound (II) or its reactive
10 derivative at the amino group or a salt thereof with the compound (IV).

This reaction can be carried out in substantially the same manner as in Example 3.

Process 3

The object compound (Ic) or a salt thereof can be prepared by reacting the compound (Id) or its reactive
15 derivative at the amino group or a salt thereof with the compound (VI).

20 This reaction can be carried out in substantially the same manner as in Example 4.

Process 4

The object compound (Ie) or a salt thereof can be
25 prepared by elimination of the amino protective group of the compound (Id) or a salt thereof.

This reaction can be carried out in substantially the same manner as in Example 6.

30 The object compound (I) and a pharmaceutically acceptable salt thereof have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism or Neurokinin B antagonism, and therefore are useful for treating or preventing Tachykinin-
35 mediated diseases, particularly Substance P-mediated

diseases, for example, respiratory diseases such as asthma, bronchitis (e.g. chronic bronchitis, acute bronchitis and diffuse panbronchiolitis, etc.), rhinitis, cough, expectoration, and the like; ophthalmic diseases such as
5 conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like; pains or aches (e.g. migraine,
10 headache, cluster headache, toothache, cancerous pain, back pain, neuralgia, etc.); and the like.

Further, it is expected that the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are useful for treating or preventing
15 ophthalmic diseases such as glaucoma, uveitis, and the like; gastrointestinal diseases such as ulcer, ulcerative colitis, irritable bowel syndrome, food allergy, and the like; inflammatory diseases such as nephritis, and the like; circulatory diseases such as hypertension, angina pectoris,
20 cardiac failure, thrombosis, Raynaud's disease, and the like; epilepsy; spastic paralysis; overactive bladder such as nervous pollakiuria, neurogenic bladder dysfunction, nocturia, unstable bladder, cystospasm, chronic cystitis (e.g. interstitial cystitis), chronic prostatitis, prostatic
25 hypertrophy, and the like; micturition disorder such as stress incontinence, urge incontinence, mixed incontinence, functional incontinence, overflow incontinence, and the like; Parkinson diseases; dementia; AIDS related dementia; Alzheimer's diseases; Down's syndrome; Huntington's chorea;
30 carcinoid syndrome; disorders related to immune enhancement or suppression; disorders caused by *Helicobacter pylori* or another spiral urease-positive gram-negative bacterium; sunburn; angiogenesis or diseases caused by angiogenesis; and the like.

It is furthermore expected that the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are useful for treating or preventing chronic obstructive pulmonary diseases, particularly chronic pulmonary emphysema; iritis; proliferative vitreoretinopathy; psoriasis; inflammatory intestinal diseases, particularly Crohn's diseases; hepatitis; superficial pain on congelation, burn, herpes zoster or diabetic neuropathy; telalgia attended to hyperlipidemia; postoperative neuroma, particularly of mastectomy; vulvar vestibulitis; hemodialysis-associated itching; lichen planus; laryngopharyngitis; bronchiectasis; coniosis; whooping cough; pulmonary tuberculosis; cystic fibrosis; emesis (e.g., nausea, retching, vomiting, acute emesis, delayed emesis, anticipatory emesis, post operative nausea and vomiting (PONV), acute and/or delayed emesis induced by drugs such as cancer chemotherapeutic agents, etc.); mental diseases, particularly anxiety disorders, stress-related disorders, affective disorders, psychological development disorders and schizophrenia; disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis; attenuation of morphine withdrawal; oedema, such as oedema caused by thermal injury; small cell carcinomas, particularly small cell lung cancer (SCLC); hypersensitivity disorders such as poison ivy; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; reflex sympathetic dystrophy such as shoulder/hand syndrome; addiction disorders such as alcoholism; stress related somatic disorders; rheumatic diseases such as fibrositis; aggressive behaviour, optionally taking an antipsychotic agent together; mania or hypomania, optionally taking an antipsychotic agent together; symptoms associated with Premenstrual Syndrome (PMS) (PMS is also now referred to as

Late Luteal Phase Syndrome (LLS); psychosomatic disorders; psychoimmunologic disorders; attention deficit disorders (ADD) with or without hyperactivity; and the like.

Furthermore, the object compound (I) and a
5 pharmaceutically acceptable salt thereof of the present invention are Central Nervous System (CNS) penetrant.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical
10 preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral, external including topical, internal, intravenous, intramuscular, inhalant,
15 nasal, intraarticular, intraspinal, transtracheal or transocular administration. The pharmaceutical preparations may be solid, semi-solid or solutions such as capsules, tablets, pellets, dragees, powders, granules, suppositories, ointments, creams, lotions, inhalants, injections,
20 cataplasms, gels, tapes, eye drops, solution, syrups, aerosols, suspension, emulsion, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

25 While the dosage of the compound (I) will vary depending upon the age and condition of a patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating Tachykinin-mediated diseases such as
30 asthma and the like. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

In order to show the utility of the object compound (I) and a pharmaceutically acceptable salt thereof, the
35 pharmacological test data of some representative compounds

of the present invention is shown in the following.

A. Emesis in the dog

5 [I] Test Method

Individually housed adult female dogs (8 to 15 kg) were given an i.v. injection of a solution containing a test compound. 5 Min later the emetic responses (retching and vomiting) were induced by administration of subcutaneous
10 apomorphine (0.1 mg/0.5 ml/kg) and observed for the next 60 min. The timing and number of retches and vomits observed were recorded for each animal. An individual animal was tested with at least 10 days between experiments.

15 [II] Test Result

The following Test Compound showed 100% inhibition rate of emesis in the dog at the dose of 1.0 mg/kg.

Test compound: The object compound of the
Example 9-(21)

20

B. Effect on cystometric parameter after lower urinary tract irritation in anesthetized guinea pigs

[I] Test Method:

25 Male Hartley guinea pigs (3-4 weeks old) were anesthetized with urethane (1.2 g/kg body weight, s.c.), and the lower abdomen was opened along the midline to expose the urinary bladder. After performing a small dissection at the apex of the bladder, a catheter was inserted into the
30 bladder. The catheter was connected through a three-way stopcock attached to a pressure transducer for measurement of intravesical pressure. A tube for drug administration was inserted into the jugular vein.

Acetic acid (0.1%) was infused at a rate of 0.3 ml/min
35 for over 30 minutes. The micturition pressure, threshold

pressure and time to the micturition (bladder capacity) were measured. After confirmation of a stable response, the mean value from the three trials was taken as the value before drug administration. Also, after drug administration the
5 mean value from the three trials for 30 minutes was taken as the value after administration. A test compound was administered intravenously at a dose of 0.1 mg/kg.

The data were analyzed by Dunnett's multiple comparison test following randomized block designed analysis of
10 variance compared with the value before drug administration.

[II] Test Result

The following test compound significantly increased bladder capacity, but did not significantly change
15 micturition pressure and threshold pressure.

Test compound: The object compound of Example 9-(24)

Some of the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are less
20 subject to metabolism in human being or animals.

The following Preparations and Examples are given for the purpose of illustrating this invention.

25 Preparation 1

1-(2-Cyclopropyl-4-isopropoxy-6-methoxy-5-pyrimidinyl)ethanol

To a solution of 2-cyclopropyl-4-isopropoxy-6-methoxy-
30 5-pyrimidinecarbaldehyde (1g) in tetrahydrofuran (20ml) was added methylmagnesium bromide (3M ethyl ether solution, 2.8 ml) dropwise with dry ice acetone bath cooling and the mixture was stirred for 2h. Hydrochloric acid (1N, 10 ml) was added to the mixture with ice bath cooling and extracted
35 with ethyl acetate, dried over magnesium sulfate, and

evaporated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of hexane and ethyl acetate (10:1) as eluent to give the title compound (1.016g) as oil.

5 IR (neat): 1564, 1117 cm^{-1}
MASS (ES^+): 275 ($\text{M}+\text{Na}$)⁺

Preparation 2

10 The following compound was obtained in substantially the same manner as that of Preparation 1.

1-(2-Ethoxy-4-isopropoxy-6-methoxy-5-pyrimidinyl)ethanol

15 MASS (ES^+): 279 ($\text{M}+\text{Na}$)⁺ and 263 (M of $\text{CHO}+\text{Na}$)

This compound was obtained as a mixture of reactant and dehydroxylated compound and was used to the next reaction without purification.

20 Preparation 3

1-(2-Cyclopropyl-4-isopropoxy-6-methoxy-5-pyrimidinyl)-1-ethanone

25 A suspension of 1-(2-cyclopropyl-4-isopropoxy-6-methoxy-5-pyrimidinyl)ethanol (0.1g), 4-methylmorpholine N-oxide (65mg) and powdered molecular sieves 4 A (0.2g) in dichloromethane (2ml) was stirred for 20min, and then tetrapropylammonium perruthenate (8.4mg) was added to the mixture with water bath cooling. The mixture was stirred
30 for 2h and was filtrated through silica gel (1g), washed with dichloromethane. The combined filtrate and washings were evaporated in vacuo to give the title compound (96.7mg) as oil.

35 IR (neat): 1705, 1695 cm^{-1}
NMR (CDCl_3 , δ): 0.95 - 1.20 (4H, m), 1.33 (6H, d, J =

6.2 Hz), 1.94 - 2.14 (1H, m), 2.46 (3H, s), 3.94 (3H, s), 5.40 (1H, septet, J = 6.3 Hz)

MASS (ES⁺): 273 (M+Na)⁺

5 Preparation 4

The following compound was obtained in substantially the same manner as that of Preparation 3.

10 1-(2-Ethoxy-4-isopropoxy-6-methoxy-5-pyrimidinyl)-ethanone

IR (neat): 1693, 1550 cm⁻¹

NMR (CDCl₃, δ): 1.37 (6H, d, J = 6.2 Hz), 1.43 (3H, d, J = 7.1 Hz), 2.45 (3H, s), 3.98 (3H, s), 4.42 (2H, q, J = 7.1 Hz), 5.43 (1H, septet, J = 6.2 Hz)

15 MASS (ES⁺): 277 (M+Na)⁺

Preparation 5

20 2-Cyclopropyl-4-isopropoxy-6-methoxy-5-pyrimidinecarboxylic acid

To a solution of 2-cyclopropyl-4-isopropoxy-6-methoxy-5-pyrimidinecarbaldehyde (0.1g) in a mixture of tert-butanol (0.5ml) and water (0.25ml) was added sulfamic acid (43mg). The resulting pale orange solution was added a solution of sodium chlorite (80%, 50mg) in water (0.2ml) with water bath cooling, and the mixture was stirred for 2.5h. Diisopropyl ether (2ml) and water (1ml) were added to the mixture and the organic layer was separated, extracted with saturated sodium hydrogen carbonate solution. The pH of the extract was made acidic with 1N hydrochloric acid, and was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and evaporated in vacuo to give the title compound (96.8mg) as solid.

mp: 120 - 121.5°C

35 IR (KBr): 1693, 1550, 1141, 1119 cm⁻¹

NMR (CDCl₃, δ): 1.00 - 1.20 (4H, m), 1.42 (6H, d, J = 6.1 Hz), 2.00 - 2.16 (1H, m), 4.06 (3H, s), 5.55 (1H, septet, J = 6.1 Hz)

MASS (ES⁻): 251 (M-H)⁺

5

Preparation 6

4,6-Diisopropoxy-2-pyrimidinamine

Sodium hydride (5.61g) was washed with hexane twice and
10 was added iso-propyl alcohol (100ml) with ice bath cooling.
To the resulting suspension was added 4,6-dichloro-2-pyrimidinamine (5g) and the mixture was stirred on 120°C bath for 2h. After cooling, the solvent was removed by
15 evaporation, and water and ethyl acetate were added to the residue. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated in vacuo to give the title compound (6.64g).

IR (neat): 1647, 1566, 1201, 1109 cm⁻¹

20 NMR (CDCl₃, δ): 1.30 (12H, d, J = 6.1 Hz), 4.75 (2H, s),
5.09 (2H, septet, J = 6.1 Hz), 5.37 (1H, s)

MASS (ES⁺): 234 (M+Na)⁺, 212 (M+H)⁺

Preparation 7

4,6-Diisopropoxy-2-pyrimidinol

25

To a solution of 4,6-diisopropoxy-2-pyrimidinamine (6.5g) in acetic acid (98ml) was added sodium nitrite (4.25g) portionwise at 20 to 28°C and the mixture was stirred at ambient temperature overnight. The mixture was
30 evaporated in vacuo, and dichloromethane (100ml), saturated sodium hydrogen carbonate solution (40ml), and 4N sodium hydroxide solution (27ml) were added successively to the residue (pH 8). The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated in
35 vacuo. The residue was purified by column chromatography on

silica gel with a mixture of dichloromethane and methanol (100:1 to 30:1) as eluent to give the title compound (2.73g) as oil.

IR (neat): 3400, 1645, 1576, 1568, 1173, 1103 cm^{-1}

5 NMR (CDCl_3 , δ): 1.35 (12H, d, $J = 6.2$ Hz), 5.07 (2H, septet, $J = 6.2$ Hz), 5.16 (1H, s)

MASS (ES^+): 235 ($\text{M}+\text{Na}$) $^+$, 213 ($\text{M}+\text{H}$) $^+$

Preparation 8

10 The following compounds were obtained in substantially the same manner as that of Preparation 7.

(1) 4-Methoxy-6-[(3S)-tetrahydro-3-furanyloxy]-2-pyrimidinol

15 mp: 183 - 185°C

IR (KBr): 1641, 1566, 1467, 1427, 1354, 1313, 1211, 1168, 1107, 1074 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.86 - 2.02 (1H, m), 2.10 - 2.32 (1H, m), 3.65 - 3.92 (4H, m), 3.81 (3H, s), 5.37 (1H, m), 5.51 (1H, s), 11.67 (1H, s)

20 MASS (ES^+): 235 ($\text{M}+\text{Na}$) $^+$, 213 ($\text{M}+\text{H}$) $^+$

(2) 4-Methoxy-6-[(3R)-tetrahydro-3-furanyloxy]-2-pyrimidinol

25 mp: 183 - 185°C

IR (KBr): 1641, 1566, 1469, 1425, 1354, 1313, 1211, 1168, 1105, 1074 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.85 - 2.04 (1H, m), 2.10 - 2.34 (1H, m), 3.64 - 3.90 (4H, m), 3.81 (3H, s), 5.37 (1H, m), 5.49 (1H, s), 11.67 (1H, s)

30 MASS (ES^+): 235 ($\text{M}+\text{Na}$) $^+$

Preparation 9

4,6-Diisopropoxy-2-methoxypyrimidine

To a solution of 4,6-diisopropoxy-2-pyrimidinol (1.04g) in N,N-dimethylformamide (10ml) was added cesium fluoride (2.23g) and methyl iodide (1.53ml) and the mixture was stirred at ambient temperature for 1.5h. The mixture was evaporated in vacuo and the residue was partitioned between water and diisopropyl ether. The organic layer was separated, washed with water, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of hexane and ethyl acetate (20:1) to give the title compound (0.31g) as oil.

IR (neat): 1593, 1577, 1365, 1176, 1105 cm^{-1}

NMR (CDCl_3 , δ): 1.33 (12H, d, $J = 6.2$ Hz), 3.93 (3H, s), 5.26 (2H, septet, $J = 6.2$ Hz), 5.59 (1H, s)

MASS (ES^+): 227 ($\text{M}+\text{H}$)⁺

Preparation 10

The following compounds were obtained in substantially the same manner as that of Preparation 9.

(1) 2-Ethoxy-4,6-diisopropoxypyrimidine

IR (neat): 1589, 1572, 1176, 1103 cm^{-1}

NMR (CDCl_3 , δ): 1.32 (12H, d, $J = 6.1$ Hz), 1.40 (3H, t, $J = 7.1$ Hz), 4.36 (2H, q, $J = 7.1$ Hz), 5.27 (2H, septet, $J = 6.1$ Hz), 5.58 (1H, s)

MASS (ES^+): 241 ($\text{M}+\text{H}$)⁺

(2) 4,6-Diisopropoxy-2-(2,2,2-trifluoroethoxy)pyrimidine

IR (neat): 1603, 1564, 1140, 1105 cm^{-1}

NMR (CDCl_3 , δ): 1.33 (12H, d, $J = 6.2$ Hz), 4.72 (2H, q, $J = 8.4$ Hz), 5.26 (2H, septet, $J = 6.1$ Hz), 5.67 (1H, s)

MASS (ES^+): 295 ($\text{M}+\text{H}$)⁺

- (3) 2,4-Dimethoxy-6-[(3R)-tetrahydro-3-furanyloxy]-pyrimidine
IR (neat): 1595, 1579, 1171 cm^{-1}
NMR (CDCl_3 , δ): 2.02 - 2.36 (2H, m), 3.80 - 4.06 (4H, m), 3.93 (3H, s), 3.96 (3H, s), 5.50 - 5.62 (1H, m), 5.72 (1H, s)
MASS (ES^+): 227 ($\text{M}+\text{H}$)⁺
- (4) 2-Ethoxy-4-methoxy-6-[(3R)-tetrahydro-3-furanyloxy]-pyrimidine
IR (neat): 1595, 1577, 1171 cm^{-1}
NMR (CDCl_3 , δ): 1.42 (3H, t, $J = 7.1$ Hz), 2.02 - 2.34 (2H, m), 3.80 - 4.06 (4H, m), 3.92 (3H, s), 4.40 (2H, q, $J = 7.1$ Hz), 5.50 - 5.62 (1H, m), 5.70 (1H, s)
MASS (ES^+): 241 ($\text{M}+\text{H}$)⁺
- (5) 4-Methoxy-6-[(3R)-tetrahydro-3-furanyloxy]-2-(2,2,2-trifluoroethoxy)pyrimidine
IR (neat): 1597, 1577, 1174 cm^{-1}
NMR (CDCl_3 , δ): 2.04 - 2.36 (2H, m), 3.80 - 4.05 (4H, m), 3.94 (3H, s), 4.75 (2H, q, $J = 8.4$ Hz), 5.50 - 5.62 (1H, m), 5.80 (1H, s)
MASS (ES^+): 295 ($\text{M}+\text{H}$)⁺
- (6) 2,4-Dimethoxy-6-[(3S)-tetrahydro-3-furanyloxy]-pyrimidine
IR (neat): 1599, 1583, 1238, 1167, 1103, 1082, 1057 cm^{-1}
NMR (CDCl_3 , δ): 2.02 - 2.36 (2H, m), 3.80 - 4.06 (4H, m), 3.93 (3H, s), 3.96 (3H, s), 5.50 - 5.62 (1H, m), 5.72 (1H, s)
MASS (ES^+): 227 ($\text{M}+\text{H}$)⁺
- (7) 2-Ethoxy-4-methoxy-6-[(3S)-tetrahydro-3-furanyloxy]-

pyrimidine

IR (neat): 1587, 1275, 1238, 1165, 1101, 1084,
1059 cm^{-1}

5 NMR (CDCl_3 , δ): 1.42 (3H, t, $J = 7.1$ Hz), 2.02 - 2.34
(2H, m), 3.80 - 4.06 (4H, m), 3.92 (3H, s), 4.38
(2H, q, $J = 7.1$ Hz), 5.50 - 5.62 (1H, m), 5.70 (1H,
s)

MASS (ES^+): 241 ($\text{M}+\text{H}$)⁺

10 (8) 4-Methoxy-6-[(3S)-tetrahydro-3-furanyloxy]-2-(2,2,2-
trifluoroethoxy)pyrimidine

IR (neat): 1599, 1565, 1265, 1238, 1124, 1063 cm^{-1}

15 NMR (CDCl_3 , δ): 2.04 - 2.36 (2H, m), 3.80 - 4.05 (4H,
m), 3.94 (3H, s), 4.75 (2H, q, $J = 8.4$ Hz), 5.50 -
5.62 (1H, m), 5.80 (1H, s)

MASS (ES^+): 295 ($\text{M}+\text{H}$)⁺

Preparation 11

4,6-Diisopropoxy-2-methoxy-5-pyrimidinecarbaldehyde

20

To a solution of 4,6-diisopropoxy-2-methoxypyrimidine
(304mg) in N, N-dimethylformamide (1.8ml) was added
phosphoryl chloride (0.21ml) with ice bath cooling under
nitrogen atmosphere and the mixture was stirred at ambient
25 temperature for 30h. Cold water (9ml) was added to the
mixture and the pH of the mixture was adjusted to 8 with 4N
sodium hydroxide solution, extracted with ethyl acetate,
washed with brine, dried over magnesium sulfate, and
evaporated in vacuo. The residue was purified by column
30 chromatography on silica gel with a mixture of hexane and
ethyl acetate (10:1) as eluent to give the title compound
(281mg).

NMR (CDCl_3 , δ): 1.40 (12H, d, $J = 6.2$ Hz), 4.00 (3H, s),
5.47 (2H, septet, $J = 6.2$ Hz), 10.20 (1H, s)

35 MASS (ES^+): 277 ($\text{M}+\text{Na}$)⁺

Preparation 12

The following compounds were obtained in substantially the same manner as that of Preparation 11.

5

- (1) 2-Ethoxy-4,6-diisopropoxy-5-pyrimidinecarbaldehyde

NMR (CDCl₃, δ): 1.40 (12H, d, J = 6.2 Hz), 1.43 (3H, t, J = 7.0 Hz), 4.43 (2H, q, J = 7.0 Hz), 5.47 (2H, septet, J = 6.2 Hz), 10.19 (1H, s)

10

MASS (ES⁺): 291 (M+Na)⁺

- (2) 4,6-Diisopropoxy-2-(2,2,2-trifluoroethoxy)-5-pyrimidinecarbaldehyde

NMR (CDCl₃, δ): 1.41 (12H, d, J = 6.2 Hz), 4.77 (2H, q, J = 8.3 Hz), 5.46 (2H, septet, J = 6.2 Hz), 10.21 (1H, s)

15

MASS (ES⁺): 345 (M+Na)⁺

- (3) 2,4-Dimethoxy-6-[(3R)-tetrahydro-3-furanyloxy]-5-pyrimidinecarbaldehyde

20

IR (neat): 1691, 1581, 1493, 1377, 1234, 1140 cm⁻¹

NMR (CDCl₃, δ): 2.16 - 2.34 (2H, m), 3.90 - 4.16 (4H, m), 4.03 (3H, s), 4.09 (3H, s), 5.64 - 5.72 (1H, m), 10.20 (1H, s)

25

MASS (ES⁺): 277 (M+Na)⁺

- (4) 2-Ethoxy-4-methoxy-6-[(3R)-tetrahydro-3-furanyloxy]-5-pyrimidinecarbaldehyde

IR (neat): 1689, 1581, 1554, 1227, 1140 cm⁻¹

30

NMR (CDCl₃, δ): 1.45 (3H, t, J = 7.0 Hz), 2.18 - 2.36 (2H, m), 3.88 - 4.14 (4H, m), 4.08 (3H, s), 4.46 (2H, q, J = 7.0 Hz), 5.65 - 5.72 (1H, m), 10.20 (1H, s)

MASS (ES⁺): 291 (M+Na)⁺

35

- (5) 4-Methoxy-6-[(3R)-tetrahydro-3-furanyloxy]-2-(2,2,2-trifluoroethoxy)-5-pyrimidinecarbaldehyde
IR (neat): 1693, 1579 cm^{-1}
NMR (CDCl_3 , δ): 2.14 - 2.44 (2H, m), 3.86 - 4.20 (4H, m), 4.10 (3H, s), 4.76 (2H, q, $J = 8.2$ Hz), 5.62 - 5.76 (1H, m), 10.21 (1H, s)
MASS (ES^+): 345 ($\text{M}+\text{Na}$)⁺
- (6) 2,4-Dimethoxy-6-[(3S)-tetrahydro-3-furanyloxy]-5-pyrimidinecarbaldehyde
IR (neat): 1689, 1583, 1493, 1375, 1234, 1136 cm^{-1}
NMR (CDCl_3 , δ): 2.18 - 2.36 (2H, m), 3.88 - 4.14 (4H, m), 4.04 (3H, s), 4.09 (3H, s), 5.64 - 5.72 (1H, m), 10.20 (1H, s)
MASS (ES^+): 277 ($\text{M}+\text{Na}$)⁺
- (7) 2-Ethoxy-4-methoxy-6-[(3S)-tetrahydro-3-furanyloxy]-5-pyrimidinecarbaldehyde
IR (neat): 1689, 1581, 1554, 1227, 1140 cm^{-1}
NMR (CDCl_3 , δ): 1.45 (3H, t, $J = 7.1$ Hz), 2.18 - 2.36 (2H, m), 3.88 - 4.14 (4H, m), 4.08 (3H, s), 4.46 (2H, q, $J = 7.1$ Hz), 5.65 - 5.72 (1H, m), 10.20 (1H, s)
MASS (ES^+): 291 ($\text{M}+\text{Na}$)⁺
- (8) 4-Methoxy-6-[(3S)-tetrahydro-3-furanyloxy]-2-(2,2,2-trifluoroethoxy)-5-pyrimidinecarbaldehyde
IR (neat): 1693, 1579 cm^{-1}
NMR (CDCl_3 , δ): 2.18 - 2.38 (2H, m), 3.86 - 4.12 (4H, m), 4.10 (3H, s), 4.80 (2H, q, $J = 8.2$ Hz), 5.64 - 5.72 (1H, m), 10.21 (1H, s)
MASS (ES^+): 345 ($\text{M}+\text{Na}$)⁺

Preparation 13

2-Cyclopropyl-4,6-diisopropoxypyrimidine

To a suspension of 2-cyclopropyl-4,6-pyrimidinediol (1g) in N, N-dimethylformamide (20ml) was added cesium fluoride (5.99g) and iso-propyl iodide (5.6g) and the mixture was stirred at 50°C bath for 21h. After cooling, the mixture was poured into water (100ml), extracted with diisopropyl ether, washed with water, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of hexane and ethyl acetate (100:1) as eluent to give the title compound (1.466g).

IR (neat): 1581, 1566, 1417, 1171, 1107 cm^{-1}

NMR (CDCl_3 , δ): 0.88 - 1.10 (4H, m), 1.31 (12H, d, $J = 6.1$ Hz), 2.00 (1H, m), 5.20 (2H, q, $J = 6.1$ Hz), 5.68 (1H, s)

MASS (ES^+): 259 ($\text{M}+\text{Na}$) $^+$, 237 ($\text{M}+\text{H}$) $^+$

Preparation 14

The following compound was obtained in substantially the same manner as that of Preparation 13.

2-Cyclopropyl-4,6-bis(2,2,2-trifluoroethoxy)pyrimidine

IR (neat): 1587, 1423, 1275, 1161 cm^{-1}

NMR (CDCl_3 , δ): 0.96 - 1.15 (4H, m), 2.05 (1H, m), 4.72 (4H, q, $J = 8.3$ Hz), 6.05 (1H, s)

MASS (ES^+): 339 ($\text{M}+\text{Na}$) $^+$

Preparation 15

4-Methoxy-6-[(3S)-tetrahydro-3-furanyloxy]-2-pyrimidinamine

Sodium hydride (1.32g) was washed with hexane twice and was suspended in xylene (10ml). To the suspension was added a solution of (3S)-tetrahydro-3-furanol (2.76g) in xylene (5ml) and the mixture was stirred for 5 min and then a

solution of 4-chloro-6-methoxy-2-pyrimidinamine (5g) in xylene (35ml) was added. The mixture was stirred at 150°C bath for 19h and cooled. Water (150ml) was added to the mixture, extracted with dichloromethane, dried over
5 magnesium sulfate, and evaporated in vacuo. The residue was triturated with a mixture of ethyl acetate and diisopropyl ether, collected by filtration, and dried to give the title compound (3.18g) as solid:

mp: 148 - 150°C

10 IR (KBr): 1641, 1577, 1171, 1105, 1078 cm⁻¹

NMR (DMSO-d₆, δ): 1.80 - 2.00 (1H, m), 2.04 - 2.26 (1H, m), 3.64 - 3.92 (4H, m), 3.75 (3H, s), 5.34 (1H, s), 5.43 (1H, m), 6.56 (2H, s)

MASS (ES⁺): 234 (M+Na)⁺

15

Preparation 16

The following compound was obtained in substantially the same manner as that of Preparation 15.

20 4-Methoxy-6-[(3R)-tetrahydro-3-furanyloxy]-2-pyrimidinamine

mp: 145 - 146°C

IR (KBr): 1635, 1577, 1173, 1107, 1078 cm⁻¹

25 NMR (DMSO-d₆, δ): 1.84 - 2.00 (1H, m), 2.10 - 2.28 (1H, m), 3.60 - 3.94 (4H, m), 3.75 (3H, s), 5.34 (1H, s), 5.40 (1H, m), 6.56 (2H, s)

Preparation 17

30 (2-Cyclopropyl-4-isopropoxy-6-methoxy-5-pyrimidinyl)methanol

To a solution of 2-cyclopropyl-4-isopropoxy-6-methoxy-5-pyrimidinecarbaldehyde (215mg) in methanol (1ml) was added sodium borohydride (17.2mg) with ice bath cooling and the
35 mixture was stirred for 10min. The solvent was removed by

evaporation and the residue was partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated in vacuo to give the title compound (215mg) as oil.

IR (neat): 3400, 1568, 1128 cm^{-1}

NMR (CDCl_3 , δ): 0.88 - 1.24 (4H, m), 1.32 (6H, d, $J = 6.1$ Hz), 2.02 (1H, m), 2.22 (1H, t, $J = 6.1$ Hz), 3.94 (3H, s), 4.59 (2H, d, $J = 6.1$ Hz), 5.36 (1H, septet, $J = 6.1$ Hz)

MASS (ES^+): 239 ($\text{M}+\text{H}$) $^+$

Preparation 18

The following compound was obtained in substantially the same manner as that of Preparation 17.

(2-Ethoxy-4-isopropoxy-6-methoxy-5-pyrimidinyl)methanol

IR (neat): 3396, 1568, 1138 cm^{-1}

NMR (CDCl_3 , δ): 1.35 (6H, d, $J = 6.1$ Hz), 1.41 (2H, t, $J = 7.1$ Hz), 2.08 (1H, brt, $J = 5.9$ Hz), 3.97 (3H, s), 4.37 (2H, q, $J = 7.1$ Hz), 4.58 (2H, d, $J = 5.9$ Hz), 5.37 (1H, septet, $J = 6.1$ Hz)

MASS (ES^+): 243 ($\text{M}+\text{H}$) $^+$

Preparation 19

5-(Chloromethyl)-2-cyclopropyl-4-isopropoxy-6-methoxypyrimidine

To a solution of (2-cyclopropyl-4-isopropoxy-6-methoxy-5-pyrimidinyl)methanol (15.6mg) in dichloromethane (0.3ml) was added thionyl chloride (14.3 μ l) with ice bath cooling, and the mixture was stirred for 20min. The mixture was added saturated sodium hydrogen carbonate solution (0.5ml), extracted with ethyl acetate, washed with brine, dried over magnesium sulfate, and evaporated in vacuo to give the title

compound (13.6mg).

IR (neat): 1566, 1190, 1111 cm^{-1}

NMR (CDCl_3 , δ): 0.88 - 1.14 (4H, m), 1.33 (6H, d, $J = 6.2$ Hz), 2.02 (1H, m), 3.95 (3H, s), 4.56 (2H, s), 5.36 (1H, septet, $J = 6.2$ Hz)

Preparation 20

The following compound was obtained in substantially the same manner as that of Preparation 19.

5-(Chloromethyl)-2-ethoxy-4-isopropoxy-6-methoxypyrimidine

IR (neat): 1579, 1198, 1111 cm^{-1}

NMR (CDCl_3 , δ): 1.36 (6H, d, $J = 6.2$ Hz), 1.41 (3H, t, $J = 7.1$ Hz), 4.00 (3H, s), 4.38 (2H, q, $J = 7.1$ Hz), 4.57 (2H, s), 5.41 (1H, septet, $J = 6.2$ Hz)

Preparation 21

5-Bromo-2-cyclopropyl-4,6-bis(2,2,2-trifluoroethoxy)-pyrimidine

To a solution of 2-cyclopropyl-4,6-bis(2,2,2-trifluoroethoxy)pyrimidine (1.26 g) in acetic acid (2.28 ml) was added N-bromosuccinimide (1.42 g), and stirred for 1.5hr at 65°C. Acetic acid was removed in vacuo. To the residue was added saturated sodium hydrogen carbonate aqueous solution, extracted with dichloromethane, washed with brine, dried over magnesium sulfate and evaporated to give a crude yellow oil. Purification by chromatography (150ml silica gel, eluent; hexane only - hexane:AcOEt=20:1) gave the title compound (900 mg) as a white solid.

NMR (CDCl_3 , δ): 1.08 (4H, d, $J=6.3$ Hz), 2.06 (1H, quint, $J=6.4$ Hz), 4.82 (4H, q, $J=8.3$ Hz)

Preparation 22

The following compounds were obtained in substantially the same manner as that of Preparation 21.

- 5 (1) 5-Bromo-2-cyclopropyl-4,6-diisopropoxypyrimidine
NMR (CDCl₃, δ): 0.90-1.10(4H, m), 1.35(12H, d, J=6.2Hz),
1.90-2.10(1H, m), 5.34(2H, sept, J=6.2Hz)
MASS(API-ES, Pos): 315.2(M+H)⁺, 317.0(M+2)⁺
- 10 (2) 5-Bromo-4-isopropoxy-6-methoxy-2-(trifluoromethyl)-
pyrimidine
NMR (CDCl₃, δ): 1.41(6H, d, J=6.5Hz), 4.09(3H, s),
5.43(1H, sept, J=6.1Hz)
- 15 (3) 2-tert-Butyl-4-isopropoxy-6-methoxypyrimidine
NMR (CDCl₃, δ): 1.34(9H, s), 1.34(6H, d, J=6.0Hz),
3.91(3H, s), 5.30(1H, sept, J=6.3Hz), 5.77(1H, s)
- 20 (4) 4-Isopropoxy-6-methoxy-2-propylpyrimidine
NMR (CDCl₃, δ): 0.98(3H, t, J=7.5Hz), 1.33(6H, d,
J=6.5Hz), 1.69-1.91(2H, m), 2.70(2H, t, J=7.5Hz),
3.91(3H, s), 5.26(1H, sept, J=6.3Hz), 5.80(1H, s)
- 25 (5) 5-Bromo-2-ethyl-4-isopropoxy-6-methoxypyrimidine
NMR (CDCl₃, δ): 1.29(3H, t, J=7.7Hz), 1.38(6H, d,
J=6.2Hz), 2.73(2H, q, J=7.6Hz), 4.01(3H, s),
5.40(1H, sept, J=5.7Hz)
- 30 (6) 5-Bromo-4-isopropoxy-6-methoxy-2-propylpyrimidine
NMR (CDCl₃, δ): 0.98(3H, t, J=7.3Hz), 1.37(6H, d,
J=6.0Hz), 1.65-1.91(2H, m), 2.68(2H, t, J=7.5Hz),
4.00(3H, s), 5.39(1H, sept, J=6.3Hz)
- 35 (7) 5-Bromo-2-tert-butyl-4-isopropoxy-6-methoxypyrimidine
NMR (CDCl₃, δ): 1.33(9H, s), 1.38(6H, d, J=6.5Hz),
4.01(3H, s), 5.37(1H, sept, J=6.3Hz)

Preparation 23

2-Cyclopropyl-4,6-bis(2,2,2-trifluoroethoxy)-5-pyrimidinecarbaldehyde

5

At below -70°C , butyllithium(1.58M solution in hexane)(1.57ml) was dropwise added to 5-bromo-2-cyclopropyl-4,6-bis(2,2,2-trifluoroethoxy)pyrimidine (888.7mg) in a mixture of ether (20ml) and tetrahydrofuran (4ml), and stirred for 1hr at the same temperature. To the reaction mixture was added isopropyl formate (1.13ml) at one portion at -70°C . After stirred at the same temperature for 30 min, the resulting mixture was quenched with hydrochloric acid (1N, 2.6ml) and water (3.4ml), then stirred for 5 min at 0°C , extracted with ethyl acetate, dried over magnesium sulfate, filtered and evaporated to give a crude yellow oil (842.8mg). Purification by chromatography(silica gel, eluent; AcOEt:hexane=1:10) gave the title compound (452.7mg) as a white solid.

20

NMR (CDCl_3 , δ): 1.00-1.30(4H, m), 2.00-2.25(1H, m), 4.90(4H, q, $J=8.2\text{Hz}$), 10.30(1H, s)

MASS (API-ES, Pos): 367.1(M+Na)⁺ (021115esip0041)

Preparation 24

25

The following compounds were obtained in substantially the same manner as that of Preparation 23.

- (1) 2-Cyclopropyl-4,6-diisopropoxy-5-pyrimidinecarbaldehyde
NMR (CDCl_3 , δ): 0.80-1.50(16H, m), 1.85-2.15(1H, m), 5.15-5.60(2H, m), 10.26(1H, s)
MASS (API-ES, Pos): 265.20(M+H)⁺

30

- (2) 4-Isopropoxy-6-methoxy-2-(trifluoromethyl)-5-pyrimidinecarbaldehyde
NMR (CDCl_3 , δ): 1.43(6H, d, $J=6.0\text{Hz}$), 4.15(3H, s),

35

5.57(1H, sept, J=6.3Hz), 10.35(1H, s)

MASS (API-ES, Pos): 287.2(M+Na)⁺

(3) 2-Ethyl-4-isopropoxy-6-methoxy-5-pyrimidinecarbaldehyde

5 NMR (CDCl₃, δ): 1.31(3H, t, J=7.5Hz), 1.39(6H, d, J=6.0Hz), 2.78(2H, q, J=7.5Hz), 4.06(3H, s), 5.53(1H, sept, J=6.1Hz), 10.3(1H, s)

MASS (API-ES, Pos): 247.2(M+Na)⁺

10 (4) 4-Isopropoxy-6-methoxy-2-propyl-5-pyrimidinecarbaldehyde

NMR (CDCl₃, δ): 0.99(3H, t, J=7.5Hz); 1.39(6H, d, J=6.0Hz), 1.70-1.93(2H, m), 2.72(2H, t, J=7.5Hz), 4.06(3H, s), 5.52(1H, sept, J=6.1Hz), 10.3(1H, s)

15 MASS (API-ES, Pos): 261.20(M+Na)⁺

(5) 2-tert-Butyl-4-isopropoxy-6-methoxy-5-pyrimidinecarbaldehyde

20 NMR (CDCl₃, δ): 1.34(9H, s), 1.41(6H, d, J=6.0), 4.06(3H, s), 5.50(1H, sept, J=6.1Hz), 10.3(1H, s)

MASS (API-ES, Pos): 275.20(M+Na)⁺

Preparation 25

4-Isopropoxy-6-methoxy-2-(trifluoromethyl)pyrimidine

25

To a solution of 6-methoxy-2-(trifluoromethyl)-4-pyrimidinol (123.1 mg) in N,N-dimethylformamide (14 ml) were added cesium fluoride (289.0 mg) and 2-iodopropane (0.187 ml), and stirred for overnight at 50°C. The reaction mixture was poured into water, and extracted with dichloromethane (10 ml x 3). The combined organic layer was washed with brine, dried over magnesium sulfate, and filtrated, and the solvent was evaporated. The residue was purified by PTLC(1mm, hexane:AcOEt=20:1) to give the title compound (206 mg) as a colorless oil.

30

35

NMR (CDCl₃, δ): 1.36(6H, d, J=6.5Hz), 3.99(3H, s),
5.35(1H, sept, J=6.1Hz), 6.09(1H, s)

Preparation 26

5 The following compound was obtained in substantially
the same manner as that of Preparation 25.

2-Ethyl-4-isopropoxy-6-methoxypyrimidine

10 NMR (CDCl₃, δ): 1.30(3H, t, J=7.5Hz), 1.33(6H, d,
J=6.0Hz), 2.75(2H, q, J=7.7Hz), 3.91(3H, s),
5.26(1H, sept, J=6.3Hz), 5.80(1H, s)

Example 1

15 (2S,3S)-N-[1-(2-Cyclopropyl-4-isopropoxy-6-methoxy-5-
pyrimidinyl)ethyl]-2-phenyl-3-piperidinamine dihydrochloride

To a solution of (2S,3S)-2-phenyl-3-piperidinamine
(47mg) and 1-(2-cyclopropyl-4-isopropoxy-6-methoxy-5-
pyrimidinyl)ethanone (67mg) in methanol (1.5ml) were added
20 sodium cyanoborohydride (85mg) and acetic acid (1 drop).
After stirring for 6 days, the mixture was evaporated in
vacuo and a mixture of water and ethyl acetate was added.
The organic layer was separated, washed with brine, dried
over potassium carbonate, and evaporated in vacuo. The
25 residue was purified by column chromatography on amino
coated silica gel with dichloromethane as eluent to give
(2S,3S)-N-[1-(2-cyclopropyl-4-isopropoxy-6-methoxy-5-
pyrimidinyl)ethyl]-2-phenyl-3-piperidinamine (47.2mg) as oil.
This compound was treated with 0.4N hydrogen chloride in
30 ethyl acetate to give the title compound (46.6mg).

NMR (DMSO-d₆, δ): 0.80 - 4.04 (26H, m), 5.06 and 5.19
(1H, septet, J = 6.2 Hz, 1:1.8), 7.05 - 7.34 (5H,
m)

MASS (ES⁺): 411 (M+H)⁺ free

Example 2

The following compound was obtained in substantially the same manner as that of Example 1.

5 (2S,3S)-N-[1-(2-Ethoxy-4-isopropoxy-6-methoxy-5-pyrimidinyl)ethyl]-2-phenyl-3-piperidinamine dihydrochloride
NMR (D₂O, δ): 1.10 - 4.95 (26H, m), 5.21 and 5.34 (1H, septet, J = 6.2 Hz), 7.20 - 7.64 (5H, m)
MASS (ES⁺): 415 (M+H)⁺ free

10

Example 3

2-Cyclopropyl-4-isopropoxy-6-methoxy-N-[(2S,3S)-2-phenyl-3-piperidinyl]-5-pyrimidinecarboxamide hydrochloride

15 To a mixture of 2-cyclopropyl-4-isopropoxy-6-methoxy-5-pyrimidinecarboxylic acid (27.5mg), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (25.4mg) and 1-hydroxybenzotriazole (14.7mg) in dichloromethane (1ml) was added a solution of (2S,3S)-2-phenyl-3-piperidinamine
20 (19.2mg) in dichloromethane (1ml). After 0.5 h stirring, the mixture was evaporated in vacuo, and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated in vacuo to give 2-cyclopropyl-4-isopropoxy-6-methoxy-N-[(2S,3S)-2-phenyl-3-piperidinyl]-5-pyrimidinecarboxamide (21mg).

25 NMR (CDCl₃, δ): 0.90 - 1.12 (4H, m), 1.30 (3H, d, J = 6.2 Hz), 1.35 (3H, d, J = 6.2 Hz), 1.50 - 1.60 (1H, m), 1.62 - 1.88 (4H, m), 1.95 - 2.08 (1H, m), 2.20 - 2.30 (1H, m), 2.80 - 2.92 (1H, m), 3.14 - 3.24 (1H, m), 3.83 (3H, s), 3.90 (1H, d, J = 1.8 Hz), 4.30 - 4.38 (1H, m), 5.40 (1H, septet, J = 6.2 Hz), 7.14 - 7.36 (5H, m)

30

35 This compound was treated with 0.4N hydrogen chloride

in ethyl acetate to give the title compound (23.0mg).

NMR (D_2O , δ): 1.00 - 4.96 (22H, m), 5.31 (1H, septet, J = 6.2 Hz), 7.28 - 7.56 (5H, m)

MASS (ES^+): 411 ($M+H$)⁺ free

5

Example 4

tert-Butyl (2S,3S)-3-[(2-cyclopropyl-4-isopropoxy-6-methoxy-5-pyrimidinyl)methoxy]-2-phenyl-1-piperidinecarboxylate

10

To a solution of tert-butyl (2S,3S)-3-hydroxy-2-phenyl-1-piperidinecarboxylate (10mg) in N, N-dimethylformamide (0.3ml) was added sodium hydride (27.8mg) and stirred for 15min. Then, a solution of 5-(chloromethyl)-2-cyclopropyl-4-isopropoxy-6-methoxypyrimidine (27.8mg) in N, N-dimethylformamide (0.3ml) and tetra-butylammonium iodide (1mg) were added to the mixture and the whole was stirred at 80°C bath for 20h. After cooling, ethyl acetate and brine were added to the mixture, and the organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography on silica gel (hexane:ethyl acetate=10:1) to give the title compound (15.2mg) as oil.

20

25

IR (neat): 1693, 1568, 1111 cm^{-1}

NMR ($CDCl_3$, δ): 0.84 - 1.10 (4H, m), 1.24 (3H, d, J = 6.2 Hz), 1.26 (3H, d, J = 6.2 Hz), 1.48 (9H, s), 1.54 - 2.10 (5H, m), 2.56 - 2.76 (1H, m), 3.72 - 3.96 (2H, m), 3.89 (3H, s), 4.49 (1H, d, J = 10.2 Hz), 4.63 (1H, d, J = 10.2 Hz), 5.31 (1H, septet, J = 6.2 Hz), 5.70 (1H, brs), 7.10 - 7.60 (5H, m)

30

MASS (ES^+): 498 ($M+H$)⁺

MASS (ES^+): 520 ($M+Na$)⁺

35

Example 5

The following compound was obtained in substantially the same manner as that of Example 4.

tert-Butyl (2S,3S)-3-[(2-ethoxy-4-isopropoxy-6-methoxy-
5 5-pyrimidinyl)methoxy]-2-phenyl-1-piperidinecarboxylate

IR (neat): 1693, 1577, 1144 cm^{-1}

NMR (CDCl_3 , δ): 1.28 (6H, d, $J = 6.2$ Hz), 1.40 (3H, t, $J = 7.1$ Hz), 1.49 (9H, s), 1.52 - 1.96 (4H, m), 2.62 - 2.74 (1H, m), 3.76 - 4.00 (2H, m), 3.91 (3H, s),
10 4.37 (2H, q, $J = 7.1$ Hz), 4.49 (1H, d, $J = 10.4$ Hz), 4.62 (1H, d, $J = 10.4$ Hz), 5.33 (1H, septet, $J = 6.2$ Hz), 5.73 (1H, brs), 7.15 - 7.60 (5H, m)

MASS (ES^+): 502 ($\text{M}+\text{H}$) $^+$

15 Example 6

2-Cyclopropyl-4-isopropoxy-6-methoxy-5-[[[(2S,3S)-2-phenyl-3-piperidinyl]oxy]methyl]pyrimidine hydrochloride

Trifluoroacetic acid (2.2ml) was added to tert-butyl
20 (2S,3S)-3-[(2-cyclopropyl-4-isopropoxy-6-methoxy-5-pyrimidinyl)methoxy]-2-phenyl-1-piperidinecarboxylate (143mg) and the resulting solution was stirred at 50°C bath for 2h. After cooling, saturated sodium hydrogen carbonate solution and ethyl acetate were added to the mixture. The
25 organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography on silica gel (dichloromethane:methanol:ammonia=12:1:0.1) to give 2-cyclopropyl-4-isopropoxy-6-methoxy-5-[[[(2S,3S)-2-phenyl-3-piperidinyl]oxy]methyl]pyrimidine (82.6mg) as oil. This oil
30 was treated with 0.4N hydrogen chloride in ethyl acetate to give its hydrochloride, and it was triturated with diisopropyl ether, filtrated, and dried to give the title compound (68.3mg).

35 IR (KBr): 1566, 1273, 1140, 1115 cm^{-1}

NMR (D₂O, δ): 1.00 - 1.36 (10H, m), 1.74 - 5.22 (15H, m), 7.06 - 7.56 (5H, m)

MASS (ES⁺): 398 (M+H)⁺

5 Example 7

The following compound was obtained in substantially the same manner as that of Example 6.

2-Ethoxy-4-isopropoxy-6-methoxy-5-[[[(2S,3S)-2-phenyl-
10 3-piperidinyl]oxy]methyl]pyrimidine

NMR (CDCl₃, δ): 1.28 (6H, d, J = 6.2 Hz), 1.36 - 1.48 (1H, m), 1.41 (3H, t, J = 7.1 Hz), 1.50 - 1.62 (1H, m), 1.80 - 1.98 (1H, m), 2.16 - 2.38 (1H, m), 2.72 - 2.84 (1H, m), 3.18 - 3.26 (1H, m), 3.62 (1H, s), 3.68 (1H, s), 3.78 (3H, s), 4.14 (1H, d, J = 11.0 Hz), 4.22 (1H, d, J = 11.0 Hz), 4.34 (2H, q, J = 7.1 Hz), 5.26 (1H, septet, J = 6.2 Hz), 7.10 - 7.38 (5H, m)

MASS (ES⁺): 402 (M+H)⁺

20 Example 8

(2S,3S)-N-[[2-Cyclopropyl-4,6-bis(2,2,2-trifluoroethoxy)-5-pyrimidinyl]methyl]-2-phenyl-3-piperidinamine dihydrochloride

25 To a solution of (2S,3S)-2-phenyl-3-piperidinamine in dichloromethane (24.9mg) was added 2-cyclopropyl-4,6-bis(2,2,2-trifluoroethoxy)-5-pyrimidinecarbaldehyde (33.9mg) at ambient temperature, and stirred for 15min, then added sodium triacetoxyborohydride (44.9mg) and stirred for
30 overnight at the same temperature. The reaction mixture was added 2ml of saturated sodium hydrogen carbonate aqueous solution, then extracted with dichloromethane (5mlx3), dried over diatomaceous earth. The organic layer was evaporated
35 under reduced pressure to give a crude yellow oil.

Purification by PLC (0.5mm, CH₂Cl₂:MeOH:NH₃aq.=20:1:01) gave colorless oil (44.3mg). To a solution of the oil in 2ml of dichloromethane was added 0.5ml of 4N-HCl in ethyl acetate at 0°C, then the volatiles were evaporated in vacuo to give the title compound (51.2mg), as a white powder.

NMR (D₂O, δ): 1.05-1.19 (4H, m), 1.85-2.14 (4H, m), 2.20-2.31 (1H, bd, J=13.6Hz), 3.13-3.24 (2H, m), 3.53-3.62 (1H, bd, J=13.2Hz), 3.65 (1H, d, J=14.3Hz), 3.74 (1H, d, J=14.6Hz), 4.46-4.58 (2H, m), 4.61 (1H, d, J=2.9Hz), 4.73-5.00 (2H, m), 7.09 (2H, d, J=7.3Hz), 7.35-7.48 (3H, m)

MASS (API-ES, Pos): 505.3 (M+H)⁺

Example 9

The following compounds were obtained in substantially the same manner as that of Example 8.

(1) (2S,3S)-N-[(2-Cyclopropyl-4-isopropoxy-6-methoxy-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine dihydrochloride

IR (KBr): 2833 - 2158, 1566, 1552, 1140 cm⁻¹

NMR (DMSO-d₆, δ): 0.85 - 1.10 (4H, m), 1.25 (6H, brs), 1.64 - 2.34 (5H, m), 3.00 - 5.22 (7H, m), 3.79 (3H, s), 7.30 - 7.85 (5H, m), 8.89 and 9.10 (1H, brs), 10.18 and 10.64 (1H, brs)

MASS (ES⁺): 397 (M+H)⁺

(2) (2S,3S)-N-[(2-Ethoxy-4-isopropoxy-6-methoxy-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine dihydrochloride

IR (KBr): 2846 - 2187, 1564, 1550, 1146, 1107 cm⁻¹

NMR (D₂O, δ): 1.29 (3H, d, J = 6.2 Hz), 1.32 (3H, d, J = 6.2 Hz), 1.39 (3H, t, J = 7.1 Hz), 2.00 - 2.52 (4H, m), 3.20 - 3.34 (1H, m), 3.60 - 3.74 (1H, m), 3.73 (3H, s), 3.96 (1H, d, J = 14.0 Hz), 4.03 (1H,

d, $J = 14.0$ Hz), 4.35 - 4.50 (2H, m), 4.68 - 5.28 (3H, m), 7.20 - 7.55 (5H, m)

MASS (ES^+): 401 ($M+H$)⁺

- 5 (3) (2S,3S)-N-[[2-Cyclopropyl-4-methoxy-6-(2,2,2-trifluoroethoxy)-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine dihydrochloride

IR (KBr): 2868 - 2180, 1566, 1142 cm^{-1}

10 NMR (D_2O , δ): 1.05 - 1.20 (4H, m), 4.92 - 2.20 (4H, m), 2.28 - 2.40 (1H, m), 3.16 - 3.30 (1H, m), 3.46 - 3.68 (3H, m), 3.74 (3H, s), 3.85 (1H, d, $J = 14.2$ Hz), 3.93 (1H, d, $J = 14.2$ Hz), 4.56 - 5.04 (3H, m), 7.12 - 7.54 (5H, m)

MASS (ES^+): 437 ($M+H$)⁺

15

- (4) (2S,3S)-N-[[2,4-Dimethoxy-6-(2,2,2-trifluoroethoxy)-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine dihydrochloride

IR (KBr): 2868 - 2171, 1579, 1387, 1144 cm^{-1}

20 NMR (D_2O , δ): 1.98 - 2.26 (3H, m), 2.44 - 2.48 (1H, m), 3.20 - 3.34 (1H, m), 3.60 - 3.72 (2H, m), 3.74 (3H, s), 3.96 (1H, d, $J = 14.2$ Hz), 4.00 (3H, s), 4.02 (1H, d, $J = 14.2$ Hz), 4.66 - 5.10 (3H, m), 7.20 - 7.58 (5H, m)

25 MASS (ES^+): 427 ($M+H$)⁺

- (5) (2S,3S)-N-[[2-Ethoxy-4-methoxy-6-(2,2,2-trifluoroethoxy)-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine dihydrochloride

30 IR (KBr): 2868 - 2187, 1579, 1144 cm^{-1}

NMR (D_2O , δ): 1.39 (3H, t, $J = 7.1$ Hz), 1.95 - 2.24 (3H, m), 2.32 - 2.46 (1H, m), 3.20 - 3.30 (1H, m), 3.60 - 3.70 (2H, m), 3.72 (3H, s), 4.38 - 4.54 (2H, m), 4.64 - 5.05 (3H, m), 7.16 - 7.56 (5H, m)

35 MASS (ES^+): 441 ($M+H$)⁺

- (6) (2S,3S)-N-[(4,6-Diethoxy-2-methoxy-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine dihydrochloride
5 IR (KBr): 2868 - 2046, 1566, 1147 cm^{-1}
NMR (D_2O , δ): 1.29 (6H, t, $J = 7.1$ Hz), 2.20 - 2.56 (2H, m), 3.20 - 3.36 (1H, m), 3.60 - 3.85 (2H, m), 3.98 (3H, s), 4.02 (1H, d, $J = 14.0$ Hz), 4.10 (1H, d, $J = 14.0$ Hz), 4.12 - 4.40 (4H, m), 4.70 - 5.00 (3H, m), 7.15 - 7.56 (5H, m)
10 MASS (ES^+): 387 ($\text{M}+\text{H}$)⁺
- (7) (2S,3S)-N-[[2,4-Dimethoxy-6-[(3R)-tetrahydro-3-furanyloxy]-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine dihydrochloride
15 NMR (D_2O , δ): 1.95 - 2.24 (4H, m), 2.28 - 2.48 (2H, m), 3.20 - 3.30 (1H, m), 3.58 - 3.70 (2H, m), 3.87 (3H, s), 3.85 - 4.00 (6H, m), 3.98 (3H, s), 4.85 (1H, m), 5.48 - 5.56 (1H, m), 7.18 - 7.28 (2H, m), 7.42 - 7.56 (3H, m)
20 MASS (ES^+): 415 ($\text{M}+\text{H}$)⁺ free
- (8) (2S,3S)-N-[[2-Ethoxy-4-methoxy-6-[(3R)-tetrahydro-3-furanyloxy]-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine dihydrochloride
25 NMR (D_2O , δ): 1.39 (3H, t, $J = 7.1$ Hz), 1.98 - 2.50 (7H, m), 3.20 - 3.32 (1H, m), 3.60 - 3.80 (2H, m), 3.76 (3H, s), 3.85 - 4.06 (6H, m), 4.38 - 4.52 (2H, m), 5.45 - 5.54 (1H, m), 7.16 - 7.28 (2H, m), 7.40 - 7.55 (3H, m)
30 MASS (ES^+): 429 ($\text{M}+\text{H}$)⁺ free
- (9) (2S,3S)-N-[[4-Methoxy-6-[(3R)-tetrahydro-3-furanyloxy]-2-(2,2,2-trifluoroethoxy)-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine dihydrochloride
35

NMR (D_2O , δ): 1.84 - 2.40 (6H, m), 3.10 - 3.28 (1H, m),
3.32 - 3.46 (1H, m), 3.50 - 4.04 (10H, m), 4.58 -
5.00 (3H, m), 5.40 - 5.52 (1H, m), 7.10 - 7.26 (2H,
m), 7.34 - 7.52 (3H, m)

5 MASS (ES^+): 483 ($M+H$)⁺ free

(10) (2S,3S)-N-[[2,4-Dimethoxy-6-[(3S)-tetrahydro-3-
furanyloxy]-5-pyrimidinyl]methyl]-2-phenyl-3-
piperidinamine dihydrochloride

10 NMR (D_2O , δ): 1.95 - 2.48 (6H, m), 3.18 - 3.30 (1H, m),
3.58 - 3.72 (2H, m), 3.75 (3H, s), 3.85 - 4.05 (9H,
m), 4.80 (1H, m), 5.44 - 5.54 (1H, m), 7.16 - 7.28
(2H, m), 7.40 - 7.58 (3H, m)

MASS (ES^+): 415 ($M+H$)⁺ free

15

(11) (2S,3S)-N-[[2-Ethoxy-4-methoxy-6-[(3S)-tetrahydro-3-
furanyloxy]-5-pyrimidinyl]methyl]-2-phenyl-3-
piperidinamine dihydrochloride

20 NMR (D_2O , δ): 1.39 (3H, t, J = 7.1 Hz), 1.94 - 2.44 (7H,
m), 3.16 - 3.30 (1H, m), 3.52 - 3.68 (2H, m), 3.66
(3H, s), 3.80 - 4.00 (6H, m), 4.43 (2H, q, J = 7.1
Hz), 5.40 - 5.50 (1H, m), 7.12 - 7.25 (2H, m),
7.36 - 7.54 (3H, m)

MASS (ES^+): 429 ($M+H$)⁺ free

25

(12) (2S,3S)-N-[[4-Methoxy-6-[(3S)-tetrahydro-3-furanyloxy]-
2-(2,2,2-trifluoroethoxy)-5-pyrimidinyl]methyl]-2-
phenyl-3-piperidinamine dihydrochloride

30 NMR (D_2O , δ): 1.90 - 2.42 (6H, m), 3.16 - 3.28 (1H, m),
3.42 - 3.66 (2H, m), 3.75 (3H, s), 3.72 - 4.00 (6H,
m), 4.66 - 5.02 (3H, m), 5.42 - 5.50 (1H, m), 7.12
- 7.24 (2H, m), 7.40 - 7.52 (3H, m)

MASS (ES^+): 483 ($M+H$)⁺ free

35 (13) (2S,3S)-N-[(4,6-Diisopropoxy-2-methoxy-5-

pyrimidinyl)methyl]-2-phenyl-3-piperidinamine
dihydrochloride

5 NMR (D_2O , δ): 1.27(6H, d, $J=6.2$ Hz), 1.30(6H, d,
 $J=6.2$ Hz), 2.00-2.16(2H, m), 2.25-2.37(1H, m),
2.46-2.55(1H, m), 3.22-3.38(1H, m), 3.65-3.74(1H,
bd, $J=13.2$ Hz), 3.76(1H, d, $J=3.7$ Hz), 3.98(3H, s),
4.00(1H, d, $J=13.9$ Hz), 4.07(1H, d, $J=13.9$ Hz),
4.92(1H, d, $J=3.3$ Hz), 5.12(2H, sept, $J=6.2$ Hz),
7.20(2H, d, $J=7.3$ Hz), 7.40-7.54(3H, m)
10 MASS (API-ES, Pos): 415.3(M+H)⁺, Free

(14) (2S,3S)-N-[(2-Ethoxy-4,6-diisopropoxy-5-
pyrimidinyl)methyl]-2-phenyl-3-piperidinamine
dihydrochloride

15 NMR (D_2O , δ): 1.26(6H, d, $J=6.2$ Hz), 1.30(6H, d,
 $J=6.2$ Hz), 1.39(3H, t, $J=7.0$ Hz), 2.02-2.14(2H, m),
2.21-2.37(1H, m), 2.50(1H, dd, $J=2.9, 3.15$ Hz),
3.22-3.35(1H, m), 3.64-3.78(2H, m), 3.98(1H, d,
 $J=13.9$ Hz), 4.05(1H, d, $J=13.9$ Hz), 4.37-4.51(2H, m),
20 4.90(1H, d, $J=3.3$ Hz), 5.10(2H, sept, $J=6.1$ Hz),
7.19(2H, d, $J=7.3$ Hz), 7.39-7.54(3H, m)
MASS (API-ES, Pos): 429.3(M+H)⁺, Free

(15) (2S,3S)-N-[(2-Cyclopropyl-4,6-diisopropoxy-5-
pyrimidinyl)methyl]-2-phenyl-3-piperidinamine
dihydrochloride

25 NMR (D_2O , δ): 1.05-1.18(4H, m), 1.24(6H, d, $J=6.2$ Hz),
1.27(6H, d, $J=6.2$ Hz), 1.96-2.12(3H, m), 2.19-
2.35(1H, m), 2.49(1H, dd, $J=3.1, 14.8$ Hz), 3.20-
30 3.35(1H, m), 3.63-3.74(2H, m), 3.97(1H, d, $J=13.5$),
4.05(1H, d, $J=13.5$ Hz), 4.87(1H, d, $J=3.7$ Hz),
5.13(2H, sept, $J=6.2$ Hz), 7.16(2H, d, $J=7.3$ Hz),
7.39-7.54(3H, m)
MASS (API-ES, Pos): 425.4(M+H)⁺, Free
35

(16) (2S,3S)-N-[[4,6-Diisopropoxy-2-(2,2,2-trifluoroethoxy)-5-pyrimidinyl]methyl]-2-phenyl-3-piperidinamine dihydrochloride

5 NMR (D₂O, δ): 1.27(6H, d, J=6.2Hz), 1.30(6H, d, J=6.2Hz), 1.99-2.17(2H, m), 2.20-2.38(1H, m), 2.43-2.56(1H, m), 3.20-3.36(1H, m), 3.63-3.79(2H, m), 3.98(1H, d, J=13.9Hz), 4.06(1H, d, J=13.9Hz), 4.85-5.05(3H, m), 5.12(2H, sept, J=6.1Hz), 7.20(2H, d, J=7.3Hz), 7.39-7.54(3H, m)

10 MASS (API-ES, Pos): 483.3(M+H)⁺, Free

(17) (2S,3S)-N-[[4,6-bis(Cyclobutyloxy)-2-methoxy-5-pyrimidinyl]methyl]-2-phenyl-3-piperidinamine dihydrochloride

15 NMR (D₂O, δ): 1.56-1.73(2H, m), 1.73-1.89(2H, m), 1.92-2.60(12H, m), 3.20-3.35(1H, m), 3.61-3.73(2H, m), 3.94(3H, s), 3.94(1H, d, J=13.5Hz), 4.00-4.03(1H, d, J=13.9Hz), 4.74-4.91(1H, m), 4.99(2H, quint, J=7.1Hz), 7.20(2H, d, J=7.3Hz), 7.40-7.54(3H, m)

20 MASS (API-ES, Pos): 439.3(M+H)⁺, Free

(18) (2S,3S)-N-[[4,6-bis(Cyclobutyloxy)-2-ethoxy-5-pyrimidinyl]methyl]-2-phenyl-3-piperidinamine dihydrochloride

25 NMR (D₂O, δ): 1.37(3H, t, J=7.3Hz), 1.57-1.72(2H, m), 1.74-1.86(2H, m), 1.95-2.14(6H, m), 2.23-2.56(6H, m), 3.30(1H, dt, J=7.7, 12.7Hz), 3.66-3.74(1H, bd, J=12.8Hz), 3.76(1H, d, J=3.7Hz), 4.02(1H, d, J=13.9Hz), 4.16(1H, d, J=13.9Hz), 4.36-4.46(2H, m), 30 4.90(1H, d, J=3.7Hz), 4.98(2H, quint, J=7.3Hz), 7.20(2H, d, J=7.3Hz), 7.41-7.54(3H, m)

MASS (API-ES, Pos): 453.3(M+H)⁺, Free

(19) (2S,3S)-N-[[4-Isopropoxy-6-methoxy-2-(trifluoromethyl)-5-pyrimidinyl]methyl]-2-phenyl-3-piperidinamine

35

dihydrochloride

NMR (D₂O, δ): 1.29(3H, d, J=6.2Hz), 1.31(3H, d, J=6.2Hz), 1.90-2.23(3H, m), 2.32-2.47(1H, m), 3.17-3.33(1H, m), 3.56(1H, s), 3.63(1H, d, J=12.8Hz), 3.82(3H, s), 3.90(1H, d, J=14.3Hz), 3.99(1H, d, J=14.3Hz), 4.55-5.07(1H, m), 5.30(1H, sept, J=6.1Hz), 7.24(2H, d, J=7.0Hz), 7.41-7.54(3H, m)

MASS (API-ES, Pos): 425.2(M+H)⁺, Free

(20) (2S,3S)-N-[(2-Ethyl-4-isopropoxy-6-methoxy-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine dihydrochloride

NMR (D₂O, δ): 1.28(3H, t, J=7.7Hz), 1.28(3H, d, J=6.2Hz), 1.31(3H, d, J=6.2Hz), 1.97-2.16(2H, m), 2.17-2.30(1H, m), 2.40-2.52(1H, m), 2.74(2H, q, J=7.6Hz), 3.19-3.35(1H, m), 3.62-3.71(2H, m), 3.75(3H, s), 3.96(1H, d, J=13.9Hz), 4.08(1H, d, J=13.9Hz), 4.85(1H, d, J=3.3Hz), 5.22(1H, sept, J=6.2Hz), 7.21(2H, d, J=7.3Hz), 7.40-7.54(3H, m)

MASS (API-ES, Pos): 385.13(M+H)⁺, Free

(21) (2S,3S)-N-[(4-Isopropoxy-6-methoxy-2-propyl-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine dihydrochloride

NMR (D₂O, δ): 0.94(3H, t, J=7.5Hz), 1.25(3H, d, J=6.2Hz), 1.29(3H, d, J=6.2Hz), 1.69-1.81(2H, m), 1.87-2.15(3H, m), 2.29-2.43(1H, bd, J=9.5Hz), 2.68(2H, t, J=7.5Hz), 3.13-3.27(1H, m), 3.30-3.39(1H, bs), 3.55-3.64(1H, bd, J=12.1Hz), 3.70(3H, s), 3.73(1H, d, J=13.9Hz), 3.85(1H, d, J=13.9Hz), 4.66(1H, d, J=2.9Hz), 5.16(1H, sept, J=6.2Hz), 7.16(2H, d, J=7.0Hz), 7.38-7.51(3H, m)

MASS (API-ES, Pos): 399.27(M+H)⁺, Free

(22) (2S,3S)-N-[(2-tert-Butyl-4-isopropoxy-6-methoxy-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine dihydrochloride

5 NMR (D₂O, δ): 1.27(3H, d, J=6.2Hz), 1.31(3H, d, J=6.2Hz), 1.34(9H, s), 1.99-2.32(3H, m), 2.41-2.54(1H, m), 3.21-3.33(1H, m), 3.60-3.80(5H, m), 4.02(1H, d, J=13.9Hz), 4.10(1H, d, J=13.9Hz), 4.73-4.93(1H, m), 5.37(1H, sept, J=6.1Hz), 7.22(2H, d, J=7.7Hz), 7.43-7.56(3H, m)
10 MASS (API-ES, Pos): 413.20 (M+H)⁺, Free

(23) (2S,3S)-N-[2,6-Dimethoxy-3-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-2-phenyl-3-piperidinamine dihydrochloride

15 IR (KBr): 2868-2187, 1498, 1196, 1170 cm⁻¹
NMR (DMSO-d₆, δ): 1.65-2.34 (4H, m), 3.00-5.10 (12H, m), 7.05 (1H, d, J=8.8Hz), 7.40-7.88 (6H, m), 8.50-11.00 (2H, brm)
20 MASS (ES⁺): 463 (M+H)⁺, Free

(24) (2S,3S)-N-[[2-Methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]-3-pyridyl]methyl]-2-phenyl-3-piperidinamine dihydrochloride

25 NMR (D₂O, δ): 1.93-2.23 (3H, m), 2.30-2.43 (1H, m), 3.22-3.35 (1H, m), 3.61-3.70 (1H, m), 3.74 (1H, d, J=3.3Hz), 3.79 (3H, s), 3.87 (1H, d, J=14.3Hz), 4.16 (1H, d, J=14.3Hz), 4.86 (1H, d, J=3.3Hz), 7.27-7.34 (2H, m), 7.45-7.52 (3H, m), 7.85 (1H, d, J=2.6Hz), 8.36 (1H, d, J=2.6Hz)
30 MASS (API-ES, Pos): 434.2 (M+H)⁺, Free

Preparation 27

Methyl 2-hydroxy-6-methoxy-3-[(trifluoroacetyl)amino]-benzoate

To a solution of methyl 2,6-dimethoxy-3-
[(trifluoroacetyl)amino]benzoate (0.2 g) in chlorobenzene (2
ml) was added a solution of boron tribromide in
chlorobenzene (1M, 0.57 ml) and the whole was stirred at
5 room temperature overnight. To the mixture were added
saturated sodium bicarbonate solution and ethyl acetate.
The organic layer was separated, washed with brine, dried
over magnesium sulfate and evaporated in vacuo. The residue
was purified by column chromatography on silica gel with a
10 mixture of hexane and ethyl acetate (3:1) as eluent to give
the title compound (48 mg).
NMR (CDCl₃, δ): 3.88 (3H, s), 3.99 (3H, s), 6.47 (1H, d,
J=9.2Hz), 8.41 (1H, d, J=9.2Hz), 8.48 (1H, br s),
12.35 (1H, s)
15 MASS (ES⁺): 316 (M+Na)

Preparation 28

Benzyl [(2S,3S)-1-[(5-oxo-4,5-dihydro-1H-1,2,4-triazol-
3-yl)methyl]-2-phenyl-3-piperidinyl]carbamate

20

To a solution of benzyl [(2S,3S)-2-phenyl-3-
piperidinyl]carbamate (100 mg) in a mixture of N,N-
dimethylformamide (0.66 ml) and water (0.01 ml) were added
potassium carbonate (27 mg) and 5-(chloromethyl)-2,4-
25 dihydro-3H-1,2,4-triazol-3-one (45 mg), and the whole was
stirred at room temperature for 1 hour. The mixture was
poured into cold water (30 ml) and stirred for 10 minutes.
The resulting precipitates was collected by filtration,
washed with water, and dried to give the title compound (108
30 mg).

MASS (ES⁺): 408 (M+H)⁺

Preparation 29

Benzyl [(2S,3S)-1-acetyl-2-phenyl-3-piperidinyl]-
35 carbamate

To a solution of benzyl [(2S,3S)-2-phenyl-3-piperidinyl]carbamate (40 mg) in pyridine (0.4 ml) was added acetic anhydride (61 μ l) and the whole was stirred 1 hour.

5 Cold water and ethyl acetate were added to the mixture, and the organic layer was separated, washed with 1N hydrochloric acid and brine, dried over magnesium sulfate, and evaporated in vacuo to give the title compound (44.4 mg).

NMR (CDCl_3 , δ): 1.46-2.14 (7H, m), 2.90-6.06 (6H, m),
10 7.10-7.50 (10H, m).

MASS (ES^+): 353 ($\text{M}+\text{H}$)⁺

Preparation 30

5-[[(2S,3S)-3-Amino-2-phenyl-1-piperidinyl]methyl]-2,4-
15 dihydro-3H-1,2,4-triazol-3-one

To a solution of 5-[[(2S,3S)-3-amino-2-phenyl-1-piperidinyl]methyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (105 mg) in methanol was hydrogenated over 10% palladium on
20 carbon (50% wet, 7 mg) under 1 atmospheric pressure for 2 days, then the catalyst was removed by filtration and the filtrate was evaporated in vacuo to give the title compound (74 mg).

MASS (ES^+): 274 ($\text{M}+\text{H}$)⁺
25

Preparation 31

The following compounds were obtained according to a similar manner to that of Preparation 30.

30 (1) (2S,3S)-1-Acetyl-2-phenyl-3-piperidinamine
MASS (ES^+): 219 ($\text{M}+\text{H}$)⁺

(2) (2S,3S)-2-Phenyl-1-(trifluoroacetyl)-3-piperidinamine
hydrochloride
35 MASS (ES^+): 295 ($\text{M}+\text{Na}$)⁺, 273 ($\text{M}+\text{H}$)⁺

Preparation 32

Benzyl [(2S,3S)-2-phenyl-1-(trifluoroacetyl)-3-piperidinyl]carbamate

5

To a mixture of benzyl [(2S,3S)-2-phenyl-3-piperidinyl]carbamate (659 mg) and N,N-diisopropylethylamine (604 mg) in dichloroethane (6 ml) was added dropwise a solution of trifluoroacetic anhydride (892 mg) in dichloromethane (1 ml) with ice salt bath cooling. After stirring at the same condition for 0.5 hour, cold water (10 ml) was added to the mixture. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of hexane and dichloromethane (1:1) as eluent to give the title compound (575 mg).

NMR (CDCl₃, δ): 1.64-2.20 (4H, m), 3.24-4.64 (4H, m), 5.07 (2H, br s), 5.29 and 5.89 (1H, d, J=6.2Hz), 7.22-7.48 (10H, m).

20

MASS (ES⁺): 429 (M+Na)⁺, 407 (M+H)⁺

Preparation 33

2,4,6-Trimethoxyaniline

25

A suspension of 1,3,5-trimethoxynitrobenzene (509 mg) and 10% palladium on carbon (50% wet) in a mixture of methanol (15 ml) and ethyl acetate (3 ml) was stirred at room temperature under hydrogen atmosphere for 6 hours. The mixture was filtered, and the filtrate was evaporated under reduced pressure to give the title compound as a brown oil (440 mg). This oil was used immediately in the next reaction because of the instability.

30

NMR (CDCl₃, δ): 3.77 (3H, s), 3.83 (6H, s), 6.17 (2H, s)

35

MASS (APCI⁺): 184.40 (M+H)⁺

Preparation 34

2,2,2-Trifluoro-N-(2,4,6-trimethoxyphenyl)acetamide

5
To a solution of 2,4,6-trimethoxyaniline (440.2 mg) in dichloromethane (4 ml) was added N,N-diisopropylethylamine (1.17 ml) and trifluoroacetic anhydride (0.475 ml) at 0°C. After stirring at room temperature for 3.5 hours, the
10 mixture was quenched with water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to give solid (610 mg), which was purified with column chromatography (silica gel 50 ml, eluted with 10% ethyl acetate/hexane (200 ml),
15 20% ethyl acetate/hexane (200 ml), and 30% ethyl acetate/hexane (200 ml)) to give the title compound as a solid (533 mg).

NMR (CDCl₃, δ): 3.82 (9H, s), 6.16 (2H, s)

MASS (ES⁺): 280.07 (M+H)⁺

20

Preparation 35

5-(Trifluoromethyl)-1-(2,4,6-trimethoxyphenyl)-1H-tetrazole

25 A solution of 2,2,2-trifluoro-N-(2,4,6-trimethoxyphenyl)acetamide (400 mg) and triphenylphosphine (1.26 g) in carbon tetrachloride (4.4 ml) was stirred under reflux for 28 hours. After cooling to room temperature, the mixture was evaporated to give oil. Sodium azide (279 mg)
30 was added to a solution of the oil in N,N-dimethylformamide (4.4 ml) at room temperature, and the mixture was stirred at room temperature overnight. The mixture was quenched with water and extracted with ethyl acetate (x 3). The combined organic layers were washed with water and brine, dried over
35 magnesium sulfate, and evaporated to give solid (2.0 g),

which was purified with column chromatography (silica gel 100 ml, eluted with 15% ethyl acetate/hexane (200 ml), 20% ethyl acetate/hexane (200 ml), and 30% ethyl acetate/hexane (400 ml)) to give the title compound as a yellow solid
5 (306.9 mg).

NMR (CDCl₃, δ): 3.75 (6H, s), 3.89 (3H, s), 6.21 (2H, s)

Preparation 36

10 2,4,6-Trimethoxy-3-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzaldehyde

To a solution of 5-(trifluoromethyl)-1-(2,4,6-trimethoxyphenyl)-1H-tetrazole (342.1 mg) in trifluoroacetic acid (5.5 ml) was added hexamethylenetetramine (331 mg) at room temperature. After stirring under reflux for 4 hours, the mixture was quenched with water and extracted with ethyl acetate (x 3). The organic layer was washed with 1N-hydrogen chloride aqueous solution (x 2), saturated sodium bicarbonate aqueous solution, and brine, respectively, dried
20 over magnesium sulfate, and evaporated to give oil, which was purified with column chromatography (silica gel 100 ml, eluted with 20% ethyl acetate/hexane (100 ml), 30% ethyl acetate/hexane (100 ml), 40% ethyl acetate/hexane (100 ml))
25 to give the title compound (221.6 mg).

IR (KBr): 1687, 1599 cm⁻¹

NMR (CDCl₃, δ): 3.74 (3H, s), 3.89 (3H, s), 4.05 (3H, s), 6.39 (1H, s), 10.35 (1H, s)

MASS (ESI⁺): 355.1 (M+Na)⁺

30

Preparation 37

2,3,6-Trimethoxy-5-nitrobenzoic acid

To a solution of 1,2,5-trimethoxybenzoic acid (2.55 g)
35 in acetic acid (6 ml) was added dropwise a solution of

nitric acid (0.9 ml) in acetic acid (3 ml) at 15-20°C. After stirring at room temperature for 1 hour, the mixture was quenched with water (18 ml). The mixture was stirred at room temperature for 30 minutes. The precipitate was
5 filtered and washed with water (10 ml x 2) and dried at room temperature overnight to give the title compound as a solid (2.1879 g).

NMR (CDCl₃, δ): 3.94 (3H, s), 3.98 (3H, s), 4.03 (3H, s), 7.62 (1H, s)

10 MASS (ES⁺): 280.1 (M+Na)⁺

Preparation 38

Methyl 2,3,6-trimethoxy-5-nitrobenzoate

15 To a solution of 2,3,6-trimethoxy-5-nitrobenzoic acid (2.36g) in N,N-dimethylformamide (24 ml) was added potassium carbonate (6.34 g) and methyl iodide (1.71 ml) at 0°C. After stirring at room temperature for 3 hours, the mixture was quenched with water and extracted with a mixture of ethyl
20 acetate and hexane (1:1), (200 ml x 3). The combined organic layers were washed with water and brine, dried over magnesium sulfate, and evaporated to give the title compound as an oil (2.842 g).

NMR (CDCl₃, δ): 3.91 (3H, s), 3.92 (3H, s), 3.96 (3H, s), 3.97 (3H, s), 7.57 (1H, s)

25 MASS (ES⁺): 294.1 (M+Na)⁺

Preparation 39

The following compound was obtained according to a
30 similar manner to that of Preparation 33.

Methyl 3-amino-2,5,6-trimethoxybenzoate

NMR (CDCl₃, δ): 3.75 (3H, s), 3.78 (3H, s), 3.80 (3H, s), 3.93 (3H, s), 6.38 (1H, s)

35 MASS (ESI⁺): 242.3 (M+H)⁺, 264.3 (M+Na)⁺

Preparation 40

The following compound was obtained according to a similar manner to that of Preparation 34.

5

Methyl 2,3,6-trimethoxy-5-[(trifluoroacetyl)amino]-benzoate

NMR (CDCl₃, δ): 3.83 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 3.96 (3H, s), 8.03 (1H, s), 8.39 (1H, br s)

10 MASS (ESI⁺): 338.3 (M+H)⁺, 360.1 (M+Na)⁺

Preparation 41

The following compound was obtained according to a similar manner to that of Preparation 35.

15

Methyl 2,3,6-trimethoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzoate

NMR (CDCl₃, δ): 3.56 (3H, s), 3.88 (3H, s), 3.97 (3H, s), 3.98 (3H, s), 6.94 (1H, s)

20 MASS (ESI⁺): 385.2 (M+Na)⁺

Preparation 42

2,3,6-Trimethoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzaldehyde

25

To a solution of methyl 2,3,6-trimethoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzoate (350 mg) in toluene (3.5 ml) was added dropwise diisobutylaluminum hydride (1.01M solution in toluene, 1.9 ml) under -60°C. The mixture was stirred at the same temperature for 15 minutes, and then quenched with saturated ammonium chloride aqueous solution (5 ml) at -60°C. The whole mixture was warmed to 0°C, and added ethyl acetate (5 ml) and 6N-hydrogen chloride aqueous solution (1.3 ml). After stirring for 10 minutes, the mixture was separated. The aqueous layer was extracted

30

35

with ethyl acetate. The combined organic layers were washed with 0.1N-hydrogen chloride aqueous solution and brine, dried over magnesium sulfate, and evaporated to give oil (291 mg). A solution of the oil (291 mg) and manganese
5 dioxide (1.47 g) in chloroform (3 ml) was stirred under reflux for 2 hours. Manganese dioxide (1.32 g) was added to the mixture, and the mixture was stirred under reflux for 3 hours. The whole mixture was filtered with celite. The filtrate was evaporated to give the title compound as a
10 solid (232.6 mg).

NMR (CDCl₃, δ): 3.62 (3H, s), 3.92 (3H, s), 4.10 (3H, s), 7.11 (1H, s), 10.43 (1H, s)

MASS (ESI⁺): 333.1 (M+H)⁺, 355.1 (M+Na)⁺

15 Preparation 43

2,4-Dimethoxy-6-(2-methoxyethoxy)benzaldehyde

A suspension of 2-hydroxy-4,6-dimethoxybenzaldehyde (200 mg), 1-chloro-2-methoxyethane (0.3 ml), potassium
20 carbonate (455 mg), and potassium iodide (545 mg) in N,N-dimethylformamide (2 ml) was stirred at 80°C for 4.5 hours. To the mixture was added 1-chloro-2-methoxyethane (0.3 ml), potassium carbonate (455 mg), and potassium iodide (545 mg), and the whole mixture was stirred at 80°C for 4.5 hours. The
25 mixture was quenched with saturated sodium bicarbonate aqueous solution, and extracted with ethyl acetate (x 2). The combined organic layers were washed with water and brine, dried over magnesium sulfate and evaporated to give, which was purified with preparative TLC (1 mm) (solvent 50% ethyl
30 acetate/hexane) to give the title compound as an oil (154.5 mg).

NMR (CDCl₃, δ): 3.45 (3H, s), 3.68-3.81 (2H, m), 3.86 (3H, s), 3.88 (3H, s), 4.10-4.20 (2H, m), 6.10 (2H, s), 10.39 (1H, s)

35 MASS (APCI⁺): 241.27 (M+H)⁺

Preparation 44

The following compound was obtained according to a similar manner to that of Preparation 43.

5

2-(2-Formyl-3,5-dimethoxyphenoxy)acetamide

NMR (DMSO-d₆, δ): 3.87 (6H, s), 4.51 (2H, s), 6.25 (1H, d, J=2.0Hz), 6.32 (1H, d, J=2.0Hz), 7.63-7.73 (2H, m), 10.23 (1H, s)

10

Preparation 45

8-(Hydroxymethyl)-7-methoxy-4-(2,2,2-trifluoroethyl)-2H-1,4-benzoxazin-3(4H)-one

15

A mixture of methyl 2-hydroxy-6-methoxy-3-[(trifluoroacetyl)amino]benzoate (141 mg) and borane-tetrahydrofuran complex (1M solution) (7.21 ml) was refluxed for 3 hours. The reaction mixture was quenched with saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate three times. The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give crude 2-hydroxy-3-hydroxymethyl-4-methoxy-N-trifluoroethylaniline (180.2 mg). To a solution of the aniline in methyl isobutyl ketone (0.7 ml) was added sodium bicarbonate (97 mg, 2.4 eq) in water (0.7 ml) and the resulting mixture was cooled in ice-bath. To the mixture was added dropwise chloroacetyl chloride, then the reaction mixture was refluxed for 4 hours. After the mixture was cooled to 20°C, it was partitioned between ethyl acetate and saturated sodium bicarbonate aqueous solution. The organic phase was washed with brine, dried over magnesium sulfate and evaporated to give a crude compound (175.3 mg). Purification by column chromatography (silica gel: ethyl acetate:hexane=2:1) gave the title compound as a white powder (95.6 mg).

35

NMR (CDCl₃, δ): 2.37 (1H, t, J=6.8Hz), 3.87 (3H, s),
4.56 (2H, q, J=8.5Hz), 4.69 (2H, s), 4.78 (2H, d,
J=6.5Hz), 6.61 (1H, d, J=9Hz), 6.95 (1H, d, J=9Hz)
MASS (API-ES, Pos): 314.2 (M+Na)⁺

5

Preparation 46

7-Methoxy-3-oxo-4-(2,2,2-trifluoroethyl)-3,4-dihydro-
2H-1,4-benzoxazine-8-carbaldehyde

10 To a solution of 8-(hydroxymethyl)-7-methoxy-4-(2,2,2-
trifluoroethyl)-2H-1,4-benzoxazin-3(4H)-one (95 mg) in
dimethyl sulfoxide (1 ml) was added a mixture of sulfur
trioxide pyridine complex (208 mg) and triethylamine (0.364
ml) in dimethyl sulfoxide (1 ml), and stirred for 30 minutes
15 at 20°C. The reaction mixture was quenched with saturated
sodium bicarbonate aqueous solution and extracted with ethyl
acetate three times. The combined extracts were washed with
brine, dried over magnesium sulfate and evaporated in vacuo
to give the title compound as a pale yellow solid (87.9 mg),
20 which was used for the next reaction without purification.

NMR (CDCl₃, δ): 3.92 (3H, s), 4.58 (2H, q, J=8.5Hz),
4.76 (2H, s), 6.68 (1H, d, J=9Hz), 7.21 (1H, d,
J=9Hz), 10.46 (1H, s)

MASS (API-ES, Nega): 288.0 (M-H)⁻

25

Preparation 47

6-Ethoxy-2,3-dihydro-1,4-benzodioxin-5-carbaldehyde

To a stirred solution of 6-ethoxy-2,3-dihydro-1,4-
30 benzodioxin (628.6 mg) in tetrahydrofuran (17 ml) were added
N,N,N',N'-tetramethylethylenediamine (3.16 ml) and 1.58M
butyllithium in hexane (6.62 ml) at -50°C under a nitrogen
atmosphere. The mixture was stirred at -50°C for 2 hours,
then N,N-dimethylformamide (1.35 ml) was added. The
35 solution was stirred at -50°C for 1 hour and allowed to warm

to 20°C. After saturated ammonium chloride aqueous solution (37 ml) was added to the reaction mixture, the mixture was extracted with ethyl acetate, washed with brine, dried over magnesium sulfate and evaporated to give a crude orange oil.

5 The crude products were purified by chromatography on silica gel (eluent, petroleum ether: diethyl ether=7:3-1:2). The solvent was evaporated. The residue was washed with petroleum ether and collected by filtration to give the title compound as a yellow solid (286 mg).

10 NMR (CDCl₃, δ): 1.43 (3H, t, J=7Hz), 4.07 (2H, q, J=7Hz), 4.2-4.28 (2H, m), 4.32-4.4 (2H, m), 6.45 (1H, d, J=9Hz), 7.01 (1H, d, J=9Hz), 10.48 (1H, s)
MASS (API-ES, Pos): 231.3 (M+Na)⁺

15 Preparation 48

2-Phenyl-N-[(2S,3S)-2-phenyl-3-piperidinyl]acetamide hydrochloride

To a solution of (2S,3S)-2-phenyl-3-piperidinamine (39.9 mg) in dichloromethane (2 ml) were added N,N-diisopropylethylamine (0.0789 ml) and phenylacetyl chloride (0.0269 ml) at 0°C. The reaction mixture was stirred for 1 hour at 20°C, then added saturated sodium bicarbonate aqueous solution, extracted with dichloromethane, dried over
25 diatomaceous earth and evaporated to give a crude compound. Purification by preparative thin-layer chromatography (eluent; dichloromethane:methanol=30:1 x 2) gave a colorless oil (16.4 mg). To a solution of the oil in 2 ml of
30 dichloromethane was added 0.5 ml of 4N-hydrogen chloride in ethyl acetate at 0°C, then the volatiles were evaporated in vacuo to give the title compound as a white powder (17.1 mg).

NMR (D₂O, δ): 1.89-2.06 (3H, m), 2.07-2.2 (1H, m),
3.19-3.34 (1H, m), 3.45 (1H, d, J=15Hz), 3.49 (1H, d, J=15Hz), 3.63 (1H, d, J=12.4Hz), 4.56-4.62 (1H, m),
35 4.68 (1H, d, J=3.3Hz), 6.98-7.05 (2H, m),

7.22-7.28 (2H, m), 7.29-7.48 (6H, m)

MASS (API-ES, Pos): 295.3 (M+H)⁺, 317.2 (M+Na)⁺ free

Preparation 49

5 (2R)-2-Phenyl-N-[(2S,3S)-2-phenyl-3-piperidinyl]-
propanamide hydrochloride

To a solution of R-(-)-2-phenylpropionic acid (23.4 mg) in dichloromethane (1 ml) were added 1-hydroxybenzotriazole
10 (21.7 mg) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.0489 ml), and the mixture was stirred for 15 minutes at ambient temperature. The mixture was added to a solution of (2S,3S)-2-phenyl-3-piperidinamine (31.6 mg) in dichloromethane (1 ml) at 0°C,
15 then stirred for 1 hour at 20°C. The reaction mixture was added saturated sodium bicarbonate aqueous solution, extracted with dichloromethane, dried over diatomaceous earth and evaporated to give a crude compound. Purification by preparative thin-layer chromatography (eluent;
20 dichloromethane:methanol=30:1 x 2) gave a white solid (29.5 mg). To a solution of the oil in 2 ml of dichloromethane was added 4N-hydrogen chloride in ethyl acetate (0.5 ml) at 0°C, then the volatiles were evaporated in vacuo to give the title compound as a white solid (31.8 mg).

25 NMR (D₂O, δ): 1.21 (3H, d, J=7Hz), 1.76-1.99 (3H, m),
2.02-2.16 (1H, m), 3.25 (1H, dt, J=3.4, 12.6Hz),
3.57-3.69 (2H, m), 4.56-4.63 (1H, m), 4.7 (1H, d, J=3.3Hz), 7.13-7.19 (2H, m), 7.28-7.4 (5H, m),
7.44-7.53 (3H, m)

30 MASS (API-ES, Pos): 309.4 (M+H)⁺ free

Preparation 50

The following compound was obtained according to a similar manner to that of Preparation 49.

(2S)-2-Phenyl-N-[(2S,3S)-2-phenyl-3-piperidinyl]-
propanamide hydrochloride

NMR (D₂O, δ): 1.31 (3H, d, J=7.3Hz), 1.86-2.06 (3H, m),
2.06-2.19 (1H, m), 3.18-3.33 (1H, m), 3.57-3.71
5 (2H, m), 4.58-4.66 (2H, m), 6.99-7.07 (2H, m),
7.07-7.14 (2H, m), 7.16-7.25 (2H, m), 7.26-7.39
(4H, m)

MASS (API-ES, Pos): 309.4 (M+H)⁺ free

10 Example 10

The following compounds were obtained according to a
similar manner to that of Example 8.

(1) (2S,3S)-N-[2,6-Dimethoxy-3-[5-(trifluoromethyl)-1H-
15 tetrazol-1-yl]benzyl]-2-phenyl-3-piperidinamine
dihydrochloride

NMR (DMSO-d₆ and D₂O, δ): 1.70-2.36 (4H, m), 3.00-5.00
(12H, m), 7.04 (1H, d, J=9Hz), 7.40-7.74 (5H, m),
7.78 (1H, d, J=9Hz)

20 MASS (ES⁺): 463 (M+H)⁺ free

(2) (2S,3S)-N-[(2-Ethoxy-4-isopropoxy-6-methoxy-5-
pyrimidinyl)methyl]-2-phenyl-3-piperidinamine
dihydrochloride

25 NMR (DMSO-d₆, δ): 1.12-1.40 (9H, m), 1.66-2.34 (4H, m),
3.00-4.00 (8H, m), 4.33 (2H, q, J=7.0Hz), 4.91 (1H,
br s), 5.14 (1H, septet, J=6.2Hz), 7.30-7.74 (5H,
m)

MASS (ES⁺): 401 (M+H)⁺ free

30

(3) (2S,3S)-1-Acetyl-N-[(2-cyclopropyl-4-isopropoxy-6-
methoxy-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine

NMR (CDCl₃, δ): 0.74-1.34 (7H, m), 1.22 and 1.25 (6H, d,
J=6.2Hz), 1.58-2.04 (5H, m), 2.09 and 2.10 (3H, s),
35 2.80-6.10 (5H, m), 3.84 and 3.86 (3H, s), 7.20-

7.64 (5H, m)

MASS (ES⁺): 461 (M+Na)⁺, 439 (M+H)⁺

- 5 (4) 5-[[(2S, 3S)-3-[[(2-Cyclopropyl-4-isopropoxy-6-methoxy-5-pyrimidinyl)methyl]amino]-2-phenyl-1-piperidinyl]-methyl]-2,4-dihydro-3H-1,2,4-triazol-3-one

MASS (ES⁺): 516 (M+Na)⁺, 494 (M+H)⁺

- 10 (5) 5-[[(2S, 3S)-3-[[2,6-Dimethoxy-3-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]amino]-2-phenyl-1-piperidinyl]-methyl]-2,4-dihydro-3H-1,2,4-triazol-3-one

NMR (CDCl₃, δ): 1.20-4.20 (14H, m), 3.33 (3H, s), 3.51 (3H, s), 6.51 (1H, d, J=8.8Hz), 7.15 (1H, d, J=8.8Hz), 7.20-7.70 (5H, m), 11.88 (1H, br s)

15 MASS (ES⁺): 582 (M+Na)⁺, 560 (M+H)⁺

- (6) 7-Methoxy-8-[[(2S, 3S)-2-phenyl-3-piperidinyl]amino]-methyl]-4-(2,2,2-trifluoroethyl)-2H-1,4-benzoxazin-3(4H)-one dihydrochloride

20 NMR (D₂O, δ): 1.97-2.25 (3H, m), 2.4-2.51 (1H, m), 3.2-3.32 (1H, m), 3.59-3.74 (5H, m), 4.14 (1H, d, J=13.5Hz), 4.25 (1H, d, J=13.5Hz), 4.46 (1H, d, J=15.4Hz), 4.63 (1H, d, J=15.4Hz), 4.69-4.88 (3H, m), 6.7 (1H, d, J=9.1Hz), 7.18-7.25 (2H, m), 7.3 (1H, d, J=9.2Hz), 7.42-7.52 (3H, m)

25 MASS (API-ES, Pos): 450.2 (M+H)⁺, 472.0 (M+Na)⁺ free

- (7) (2S, 3S)-N-[(2,4-Dimethoxy-3-pyridyl)methyl]-2-phenyl-3-piperidinamine trihydrochloride

30 NMR (D₂O, δ): 2.04-2.14 (2H, m), 2.2-2.34 (1H, m), 2.45-2.56 (1H, m), 3.25-3.36 (1H, m), 3.68 (1H, d, J=13.2Hz), 3.73 (3H, s), 3.82 (3H, s), 3.88-3.94 (1H, m), 4.18 (1H, d, J=13.6Hz), 4.27 (1H, d, J=13.5Hz), 4.94 (1H, d, J=4Hz), 6.79 (1H, d, J=6.2Hz), 7.26 (2H, d, J=7.3Hz), 7.45-7.58 (3H, m),

35

8.03 (1H, d, J=6.2Hz)

MASS (API-ES, Pos): 328.3 (M+H)⁺ free

- 5 (8) (2S,3S)-N-[2,4-Dimethoxy-6-(2-methoxyethoxy)benzyl]-2-phenyl-3-piperidinamine dihydrochloride

NMR (D₂O, δ): 2-2.15 (2H, m), 2.16-3.32 (1H, m), 2.45-2.56 (1H, m), 3.2-3.35 (1H, m), 3.44 (3H, s), 3.62 (3H, s), 3.63-3.7 (1H, m), 3.71-3.83 (3H, m), 3.87 (3H, s), 3.99-4.07 (1H, m), 4.08-4.17 (2H, m), 4.25 (1H, d, J=13.5Hz), 4.79-4.86 (1H, m), 6.16 (1H, d, J=1.8Hz), 6.19 (1H, d, J=1.8Hz), 7.17 (2H, d, J=7.7Hz), 7.4-7.6 (3H, m)

MASS (API-ES, Pos): 401.4 (M+H)⁺, 423.3 (M+Na)⁺ free

- 15 (9) 2-[3,5-Dimethoxy-2-[[[(2S,3S)-2-phenyl-3-piperidinyl]amino]methyl]phenoxy]acetamide dihydrochloride

NMR (D₂O, δ): 2.02-2.17 (2H, m), 2.21-2.33 (1H, m), 2.46-2.56 (1H, m), 3.24-3.36 (1H, m), 3.61-3.7 (4H, m), 3.84 (3H, s), 3.92-3.99 (1H, m), 4.23 (1H, d, J=13.6Hz), 4.26 (1H, d, J=13.5Hz), 4.48 (1H, d, J=15.4Hz), 4.58 (1H, d, J=15.8Hz), 4.95 (1H, d, J=4Hz), 6.1 (1H, d, J=2.2Hz), 6.24 (1H, d, J=2.2Hz), 7.28 (2H, d, J=7.7Hz), 7.45-7.59 (3H, m)

25 MASS (API-ES, Pos): 400.3 (M+H)⁺, 422.2 (M+Na)⁺ free

- (10) (2S,3S)-N-(4-Isopropoxy-2,6-dimethoxybenzyl)-2-phenyl-3-piperidinamine dihydrochloride

30 NMR (D₂O, δ): 1.36 (3H, d, J=5.9Hz), 1.37 (3H, d, J=5.5Hz), 2.02-2.12 (2H, m), 2.16-2.31 (1H, m), 2.44-2.54 (1H, m), 3.22-3.32 (1H, m), 3.6-3.71 (7H, m), 3.77-3.83 (1H, m), 4.14 (1H, d, J=13.5Hz), 4.26 (1H, d, J=13.5Hz), 4.69-4.8 (1H, m), 4.85 (1H, d, J=4Hz), 6.17 (2H, s), 7.18 (2H, d, J=7.3Hz), 7.42-7.57 (3H, m)

35

MASS (API-ES, Pos): 385.3 (M+H)⁺ free

- 5 (11) (2S,3S)-2-Phenyl-N-[2,4,6-trimethoxy-3-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-3-piperidinamine dihydrochloride

10 NMR (D₂O, δ): 1.96-2.33 (3H, m), 2.39-2.51 (1H, m), 3.22-3.36 (1H, m), 3.37-3.49 (3H, m), 3.5-3.74 (4H, m), 3.84 (3H, s), 3.87-4.26 (3H, m), 4.87-4.96 (1H, m), 6.47-6.52 (1H, m), 7.2-7.41 (2H, m), 7.48-7.61 (3H, m)

MASS (API-ES, Pos): 493.3 (M+H)⁺ free

- 15 (12) (2S,3S)-2-Phenyl-N-[2,3,6-trimethoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-3-piperidinamine dihydrochloride

20 NMR (D₂O, δ): 1.94-2.25 (3H, m), 2.35-2.46 (1H, m), 3.22-3.35 (4H, m), 3.6-3.72 (2H, m), 3.75 (3H, s), 3.85 (3H, s), 4 (1H, d, J=13.6Hz), 4.16 (1H, d, J=13.5Hz), 4.88 (1H, d, J=3.7Hz), 7.28-7.35 (3H, m), 7.47-7.55 (3H, m)

MASS (API-ES, Pos): 493.3 (M+H)⁺ free

- 25 (13) (2S,3S)-N-(2-Isopropoxy-4,6-dimethoxybenzyl)-2-phenyl-3-piperidinamine dihydrochloride

30 NMR (D₂O, δ): 1.25 (3H, d, J=6.2Hz), 1.29 (3H, d, J=6.2Hz), 2.01-2.15 (2H, m), 2.19-2.34 (1H, m), 2.47-2.58 (1H, m), 3.2-3.34 (1H, m), 3.59 (3H, s), 3.64-3.73 (1H, m), 3.74-3.8 (1H, m), 3.86 (3H, s), 4.13 (1H, d, J=13.2Hz), 4.28 (1H, d, J=13.2Hz), 4.57 (1H, sept., J=6Hz), 4.85 (1H, d, J=4Hz), 6.12 (1H, d, J=1.8Hz), 6.23 (1H, d, J=2.2Hz), 7.12 (2H, d, J=7.7Hz), 7.4-7.55 (3H, m)

MASS (API-ES, Pos): 385.3 (M+H)⁺ free

- 35 (14) (2S,3S)-N-[(6-Methoxy-2,3-dihydro-1,4-benzodioxin-5-

yl)methyl]-2-phenyl-3-piperidinamine dihydrochloride

NMR (D₂O, δ): 1.96-2.25 (3H, m), 2.42-2.53 (1H, m),
3.21-3.31 (1H, m), 3.58 (3H, s), 3.6-3.67 (1H, m),
3.74-3.81 (1H, m), 4.06-4.23 (6H, m), 4.85 (1H, d,
J=4Hz), 6.49 (1H, d, J=9.2Hz), 6.92 (1H, d,
J=9.2Hz), 7.27 (2H, d, J=7Hz), 7.46-7.57 (3H, m)

MASS (API-ES, Pos): 355.3 (M+H)⁺ free

(15) (2S,3S)-N-[(6-Ethoxy-2,3-dihydro-1,4-benzodioxin-5-

yl)methyl]-2-phenyl-3-piperidinamine dihydrochloride

NMR (D₂O, δ): 1.22 (3H, t, J=7Hz), 1.86-2.13 (3H, m),
2.35-2.48 (1H, m), 3.12-3.23 (1H, m), 3.43-3.5 (1H,
m), 3.52-3.62 (1H, m), 3.76-4.06 (5H, m), 4.08-
4.22 (3H, m), 4.64 (1H, d, J=3.3Hz), 6.49 (1H, d,
J=9.1Hz), 6.86 (1H, d, J=8.8Hz), 7.16-7.26 (2H, m),
7.42-7.52 (3H, m)

MASS (API-ES, Pos): 369.2 (M+H)⁺, 391.3 (M+Na)⁺ free

Example 11

To a solution of cis-2-phenyl-3-piperidinamine (30 mg)
in dichloromethane (0.7 ml) were added 2-cyclopropyl-4-
isopropoxy-6-methoxy-5-pyrimidinecarbaldehyde (40 mg) and
sodium triacetoxyborohydride (55 mg), and the whole was
stirred at room temperature overnight. To the mixture were
added saturated sodium bicarbonate solution and ethyl
acetate, the organic layer was separated and the aqueous
layer was extracted with ethyl acetate. The combined
organic layer was dried over potassium carbonate and
evaporated in vacuo. The residue was purified by
preparative thin layer chromatography
(dichloromethane:methanol:conc. ammonia=12:1:0.1) to give
cis-N-[(2-cyclopropyl-4-isopropoxy-6-methoxy-5-
pyrimidinyl)methyl]-2-phenyl-3-piperidinamine (63 mg). A
solution of this amine in methanol was added 4N-hydrogen
chloride in ethyl acetate (0.15 ml) and evaporated in vacuo.

This process caused des-methylation of the methoxy group, so the salt was made free by saturated sodium bicarbonate and was again purified by column chromatography to give Compound 1 of cis-N-[(2-cyclopropyl-4-isopropoxy-6-methoxy-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine (30.4 mg) and Compound 2 of 2-cyclopropyl-6-isopropoxy-5-[[[cis-2-phenyl-3-piperidinyl]amino]methyl]-4-pyrimidinol (27.6 mg). The obtained amines were converted into their dihydrochlorides each with 0.4N-hydrogen chloride in ethyl acetate.

10 Dihydrochloride of Compound 1

NMR (DMSO-d₆, δ): 0.85-1.10 (4H, m), 1.30 (6H, br s), 1.70-2.30 (5H, m), 3.10-5.20 (10H, m), 7.35-7.65 (5H, m)

MASS (ES⁺): 397 (M+H)⁺ free

15

Dihydrochloride of Compound 2

NMR (DMSO-d₆, δ): 0.90-1.60 (10H, m), 1.75-2.30 (5H, m), 3.05-5.45 (7H, m), 7.40-7.65 (5H, m)

MASS (ES⁺): 383 (M+H)⁺ free

20

Example 12

The following compounds were obtained according to a similar manner to that of Example 3.

- 25 (1) 2-Cyclopropyl-4-isopropoxy-6-methoxy-N-[(2S,3S)-2-phenyl-1-(trifluoroacetyl)-3-piperidinyl]-5-pyrimidinecarboxamide

mp: 164-165°C

30 NMR (CDCl₃, δ): 0.92-1.10 (4H, m), 1.16 (6H, d, J=6.2Hz), 1.78-4.70 (11H, m), 5.29 (1H, septet, J=6.2Hz), 5.59 and 5.95 (1H, d, J=6.2Hz), 6.32 (1H, d, J=8.2Hz), 7.30-7.58 (5H, m)

MASS (ES⁺): 529 (M+Na)⁺, 507 (M+H)⁺

- 35 (2) 2-Cyclopropyl-4-isopropoxy-6-methoxy-N-[(2S,3S)-1-[(5-

oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]-2-phenyl-3-piperidinyl]-5-pyrimidinecarboxamide

MASS (ES⁺): 530 (M+Na)⁺, 508 (M+H)⁺

5 Example 13

2-Cyclopropyl-4-isopropoxy-6-methoxy-N-[(2S,3S)-2-phenyl-3-piperidinyl]-5-pyrimidinecarboxamide hydrochloride

To a solution of 2-cyclopropyl-4-isopropoxy-6-methoxy-
10 N-[(2S,3S)-2-phenyl-1-(trifluoroacetyl)-3-piperidinyl]-5-pyrimidinecarboxamide (4.2 mg) in methanol (0.8 ml) was added 10% potassium carbonate solution (0.5 ml) and the whole was stirred at 40°C bath for 1.5 hours. After cooling, the solvent was removed by evaporation and the residue was
15 partitioned between ethyl acetate and brine. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated in vacuo to give the title compound (3.0 mg).

NMR (CDCl₃, δ): 0.90-1.12 (4H, m), 1.30 (3H, d, J=6.2Hz), 1.35 (3H, d, J=6.2Hz), 1.50-1.60 (1H, m), 1.62-1.88 (4H, m), 1.95-2.08 (1H, m), 2.20-2.30 (1H, m), 2.80-2.92 (1H, m), 3.14-3.24 (1H, m), 3.83 (3H, s), 3.90 (1H, d, J=1.8Hz), 4.30-4.38 (1H, m), 5.40 (1H, septet, J=6.2Hz), 7.14-7.36 (5H, m)

25

Example 14

Compound A

(2S,3S)-N-[[3-Methoxy-6-[5-(trifluoromethyl)-1H-tetrazol-1-yl]-2-pyridyl)methyl]-2-phenyl-3-piperidinamine
30 trihydrochloride

Compound B

(2S,3S)-N,1-bis[[3-Methoxy-6-[5-(trifluoromethyl)-1H-tetrazol-1-yl]-2-pyridyl)methyl]-2-phenyl-3-piperidinamine
35 tetrahydrochloride

Compound C

(2S,3S)-1-[[3-Methoxy-6-[5-(trifluoromethyl)-1H-tetrazol-1-yl]-2-pyridyl]methyl]-2-phenyl-3-piperidinamine
5 trihydrochloride

To a solution of (2S,3S)-2-phenyl-3-piperidinamine (27.1 mg) in dichloromethane (0.5 ml) was added 2-(bromomethyl)-3-methoxy-6-[5-(trifluoromethyl)-1H-tetrazol-1-yl]pyridine (51.7 mg) and N,N-diisopropylethylamine (37.5 μ l) at ambient temperature, then stirred for overnight at the same temperature. The reaction mixture was added saturated sodium bicarbonate aqueous solution (2 ml), then extracted with dichloromethane (5 ml x 3), and dried over diatomaceous
15 earth. The organic layer was evaporated under reduced pressure to give a crude yellow oil. Purification by preparative thin-layer chromatography (eluent: dichloromethane:methanol:ammonia water=30:1:0.1) gave three compounds. To a solution of each compound in
20 dichloromethane (2 ml) was added 4N-hydrogen chloride in ethyl acetate (0.5 ml) at 0°C, then the volatiles were evaporated in vacuo to give each hydrochloride salt of the title compounds as a pale yellow solid (Compound A: 11.2 mg, Compound B: 26.2 mg, Compound C: 26.0 mg).

25 Compound A

NMR (D_2O , δ): 1.91-2.03 (1H, m), 2.03-2.22 (2H, m),
2.32-2.44 (1H, m), 3.22-3.33 (1H, m), 3.57-3.67
(1H, m), 3.7-3.78 (1H, m), 3.85 (3H, s), 4.04 (1H,
d, J=15.7Hz), 4.25 (1H, d, J=15.7Hz), 4.85 (1H, d,
30 J=3.6Hz), 7.3-7.37 (2H, m), 7.4-7.46 (3H, m), 7.65
(1H, d, J=8.8Hz), 7.81 (1H, d, J=8.8Hz)

MASS (API-ES, Pos): 434.4 (M+H)⁺ free

Compound B

35 NMR (D_2O , δ): 1.78-2.25 (3H, m), 2.27-2.43 (1H, m),

2.86-3.1 (1H, m), 3.38-3.55 (1H, m), 3.73-3.83 (1H, m), 3.86 (3H, s), 3.88-3.99 (4H, m), 4.13 (1H, d, J=15Hz), 4.16 (1H, d, J=16.4Hz), 4.41 (1H, d, J=8.8Hz)

5 MASS (API-ES, Pos): 691.2 (M+H)⁺ free

Compound C

NMR (D₂O, δ): 1.75-1.97 (2H, m), 2.02-2.25 (2H, m),
2.85 (1H, br s), 3.41 (1H, d, J=12.1Hz), 3.74-3.83
10 (1H, m), 3.83-3.94 (4H, m), 4.19 (1H, d, J=16.1Hz),
4.39 (1H, br s), 7.35-7.55 (5H, m), 7.68 (1H, d, J=8.8Hz), 7.81 (1H, d, J=8.8Hz)

MASS (API-ES, Pos): 434.2 (M+H)⁺ free

15 Example 15

(2S,3S)-N-[(2-Ethoxy-4-isopropoxy-6-methoxy-5-pyrimidinyl)methyl]-2-phenyl-1-(trifluoroacetyl)-3-piperidinamine

20 To a suspension of (2S,3S)-2-phenyl-1-(trifluoroacetyl)-3-piperidinamine hydrochloride (50 ml) in dichloromethane (10 ml) was added saturated sodium bicarbonate aqueous solution (10 ml), and stirred for 5 minutes. The organic layer was separated, washed with brine,
25 dried over magnesium sulfate and evaporated to give a free amine (45 mg). To a solution of the free amine (45 mg) in dichloromethane (0.5 ml) was added 2-ethoxy-4-isopropoxy-6-methoxy-5-pyrimidinecarbaldehyde (38.9 mg) at ambient temperature, and stirred for 15 minutes, then added sodium
30 triacetoxyborohydride (51.5 mg) and stirred for overnight at the same temperature. The reaction mixture was added 2 ml of saturated sodium bicarbonate aqueous solution, then extracted with dichloromethane (5 ml x 3), and dried over diatomaceous earth. The organic layer was evaporated under
35 reduced pressure to give a crude colorless oil (83.3 mg).

Purification by preparative thin-layer chromatography (eluent: ethyl acetate:hexane=1:2) gave the title compound (78.9 mg).

5 NMR (CDCl₃, δ): 1.24 (3H, d, J=2.2Hz), 1.26 (3H, d, J=2.2Hz), 1.40 (3Hx4/5, t, J=7.1Hz), 1.41 (3Hx1/5, t, J=7.1Hz), 1.62-2.09 (4H, m), 2.79-2.90 (1Hx1/5, m), 2.99-3.13 (1H, m), 3.15-3.27 (1Hx4/5, m), 3.64-3.78 (2H+1Hx4/5, m), 3.87 (3Hx4/5, s), 3.89 (3Hx1/5, s), 4.28-4.4 (2H+1Hx1/5, m), 5.23-5.37 (1H+1Hx1/5, m), 5.94 (1Hx4/5, d, J=5.5Hz), 7.25-7.38 (3H, m), 7.57 (2Hx4/5, d, J=7.3Hz), 7.69 (2Hx1/5, d, J=7.3Hz)

10 MASS (API-ES, Pos): 519.2 (M+Na)⁺

15 Example 16

(2S,3S)-N-[(2-Ethoxy-4-isopropoxy-6-methoxy-5-pyrimidinyl)methyl]-N-methyl-2-phenyl-1-(trifluoroacetyl)-3-piperidinamine

20 To a solution of (2S,3S)-N-[(2-ethoxy-4-isopropoxy-6-methoxy-5-pyrimidinyl)methyl]-2-phenyl-1-(trifluoroacetyl)-3-piperidinamine (10 mg) in dichloromethane (0.2 ml) and methanol (0.02 ml) was added formaldehyde 37 wt% solution in water (7.5 μ l) at 20°C, and stirred for 30 minutes at the same temperature, then added sodium triacetoxyborohydride (42.7 mg) at 0°C and stirred for 1 hour at 20°C. The reaction mixture was added with 2 ml of saturated sodium bicarbonate aqueous solution, then extracted with dichloromethane (5 ml x 3), dried over diatomaceous earth. 30 The organic layer was evaporated under reduced pressure to give the title compound as a crude white foam (10.9 mg), that was used crude in the next reaction.

35 NMR (CDCl₃, δ): 1.22 (3Hx3/10, d, J=5.9Hz), 1.26 (3Hx7/10, d, J=6.2Hz), 1.28 (3Hx3/10, d, J=6.2Hz), 1.31 (3Hx7/10, d, J=5.9Hz), 1.41 (3H, t, J=7.1Hz),

1.59-1.71 (1H, m), 1.73-1.86 (1H, m), 1.9-2.09 (1H, m), 2.16 (3Hx3/10, s), 2.18 (3Hx7/10, s), 2.2-2.33 (1H, m), 2.65-2.77 (1H, m), 2.79-2.86 (1Hx3/10, m), 2.93-3.05 (1Hx7/10, m), 3.45 (1Hx3/10, d, J=12.4Hz), 3.49 (1Hx7/10, d, J=12.8Hz), 3.54 (1Hx3/10, d, J=12.4Hz), 3.59 (1Hx7/10, d, J=12.8Hz), 3.71 (1Hx7/10, d, J=14.2Hz), 3.77 (3Hx3/10, s), 3.82 (3Hx7/10, s), 4.27-4.35 (1Hx3/10, m), 4.36 (2H, q, J=7.1Hz), 5.33 (1H, sept., J=6.2Hz), 5.59 (1Hx3/10, d, J=3.7Hz), 6.23 (1Hx7/10, d, J=4.4Hz), 7.2-7.34 (3H, m), 7.72 (2Hx7/10, d, J=8Hz), 7.78 (2Hx3/10, d, J=7.7Hz).

Example 17

(2S,3S)-N-[(2-Ethoxy-4-isopropoxy-6-methoxy-5-pyrimidinyl)methyl]-N-methyl-2-phenyl-3-piperidinamine dihydrochloride.

To a solution of (2S,3S)-N-[(2-ethoxy-4-isopropoxy-6-methoxy-5-pyrimidinyl)methyl]-N-methyl-2-phenyl-1-(trifluoroacetyl)-3-piperidinamine (63.7 mg) in methanol (1.2 ml) was added 20% potassium carbonate aqueous solution (1.2 ml), and stirred for 10 hours at 60°C. The reaction mixture was extracted with dichloromethane, dried over diatomaceous earth and evaporated to give a crude compound. Purification by preparative thin-layer chromatography (eluent: dichloromethane:methanol:ammonia water=20:10:1) gave free base as an oil. To a solution of the oil in 2 ml of dichloromethane was added 4N-hydrogen chloride in ethyl acetate (0.5 ml) at 0°C, then the volatiles were evaporated in vacuo to give the title compound as a yellow solid (42.7 mg).

NMR (D₂O, δ): 1.3 (3H, d, J=5.8Hz), 1.31 (3H, d, J=5.9Hz), 1.35 (3H, t, J=7Hz), 1.94-2.12 (1H, m), 2.3-2.43 (1H, m), 2.43-2.56 (1H, m), 2.58-2.69 (1H,

m), 2.73 (3H, s), 3.23-3.35 (1H, m), 3.39-3.52 (1H, m), 3.76 (3H, s), 3.94 (1H, d, J=13.2Hz), 4-4.1 (1H, m), 4.26 (1H, d, J=13.2Hz), 4.44 (2H, q, J=7.1Hz), 5.25 (1H, d, J=5.5Hz), 5.32 (1H, d, J=6.2Hz), 7.6-7.72 (3H, m), 7.78 (2H, d, J=6.9Hz)

5 MASS (API-ES, Pos): 415.5 (M+H)⁺ free

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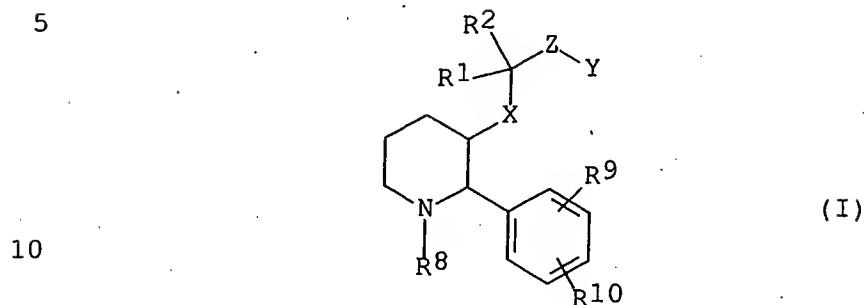
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C L A I M S

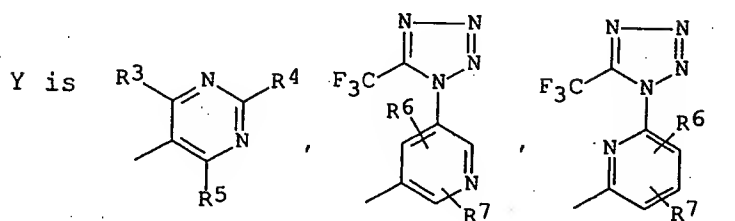
1. A compound of the formula (I):



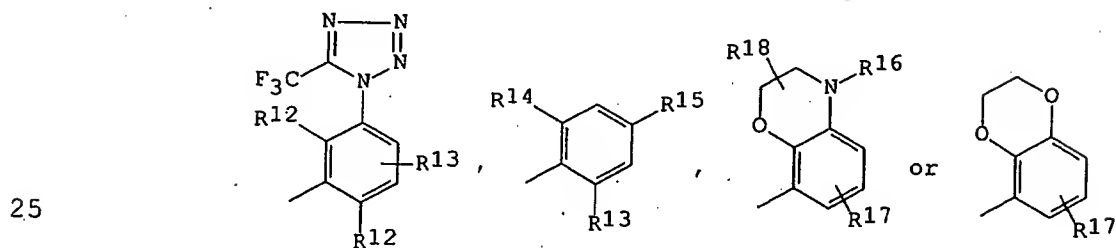
wherein

-X- is -NH or -O-;

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


(in which R³, R⁴ and R⁵ are independently hydrogen,
lower alkyl, mono(or di or
tri)halo(lower)alkyl,
cyclo(lower)alkyl, lower alkoxy,
mono(or di or tri)halo(lower)alkoxy,
cyclo(lower)alkyloxy or
tetrahydrofranyloxy;
R⁶, R⁷ and R¹⁷ are independently hydrogen
or lower alkoxy;

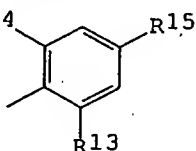
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
R^{12} is lower alkoxy;
 R^{13} is hydrogen or lower alkoxy;
 R^{14} is hydrogen or lower
 alkoxy(lower)alkoxy or
 carbamoyl(lower)alkoxy;
 R^{15} is hydrogen or isopropoxy;
 R^{16} is hydrogen or mono(or di or
 tri)halo(lower)alkyl; and
 R^{18} is hydrogen or oxo);

-Z- is bond or 

(in which R^{11} is hydrogen or lower alkyl),
 R^1 and R^2 are independently hydrogen or lower alkyl, or
 join together to form oxo;
 R^8 is hydrogen, (5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-
 yl)methyl or an amino protective group; and
 R^9 and R^{10} are independently hydrogen, halogen, lower
 alkyl or lower alkoxy, and

provided that when Y is  (in which

R^{13} , R^{14} and R^{15} are each as
 defined above, then

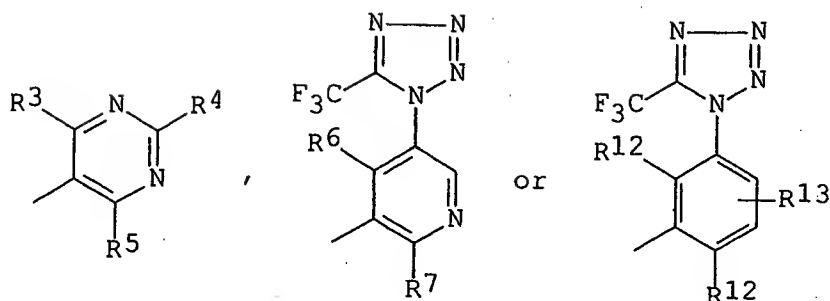
-Z- is  (in which R^{11} is
 as defined above),

and a salt thereof.

2. The compound of claim 1, in which
 -X- is -NH or -O-;

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Y is



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(in which R³, R⁴ and R⁵ are independently hydrogen,
 lower alkyl, cyclo(lower)alkyl,
 lower alkoxy or cyclo(lower)alkoxy;
 R⁶ and R⁷ are independently hydrogen or
 lower alkoxy;
 R¹² is lower alkoxy; and
 R¹³ is hydrogen or lower alkoxy);

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-Z- is bond;

R¹ and R² are independently hydrogen or lower alkyl;

R⁸ is hydrogen; and

R⁹ and R¹⁰ are each hydrogen.

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3. A compound of claim 2, which is selected from a group consisting of

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- (1) (2S,3S)-N-[(2-Cyclopropyl-4-isopropoxy-6-methoxy-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine,
- (2) (2S,3S)-N-[(2-Ethoxy-4-isopropoxy-6-methoxy-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine,
- (3) (2S,3S)-N-[(4-Isopropoxy-6-methoxy-2-propyl-5-pyrimidinyl)methyl]-2-phenyl-3-piperidinamine,
- (4) (2S,3S)-N-[2,6-Dimethoxy-3-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-2-phenyl-3-piperidinamine,
 and
- (5) (2S,3S)-N-[[2-Methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]-3-pyridyl]methyl]-2-phenyl-3-piperidinamine,

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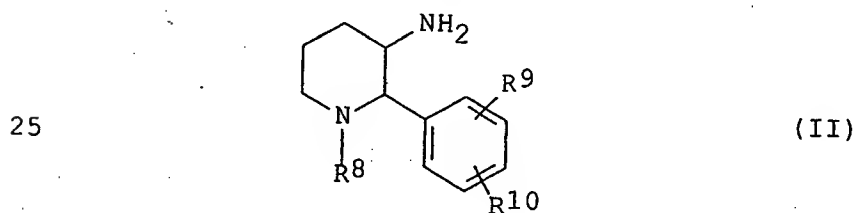
or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1, which is selected from a group consisting of

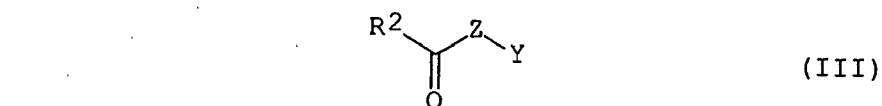
- 5 (1) (2S,3S)-N-[[3-Methoxy-6-[5-trifluoromethyl]-1H-tetrazol-1-yl]-2-pyridyl)methyl]-2-phenyl-3-piperidinamine,
 - (2) 2-[3,5-Dimethoxy-2-[[[(2S,3S)-2-phenyl-3-piperidinyl]amino]methyl]phenoxy]acetamide,
 - 10 (3) (2R)-2-Phenyl-N-[(2S,3S)-2-phenyl-3-piperidinyl]propanamide,
 - (4) 7-Methoxy-8-[[[(2S,3S)-2-phenyl-3-piperidinyl]-amino]methyl]-4-(2,2,2-trifluoroethyl)-2H-1,4-benzoxazin-3(4H)-one, and
 - 15 (5) (2S,3S)-N-[(6-Methoxy-2,3-dihydro-1,4-benzodioxin-5-y)methyl]-2-phenyl-3-piperidinamine,
- or a pharmaceutically acceptable salt thereof.

5. A process for the preparation of the compound of claim 1, or a salt thereof, which comprises,

- 20 (1) reacting a compound of the formula (II):

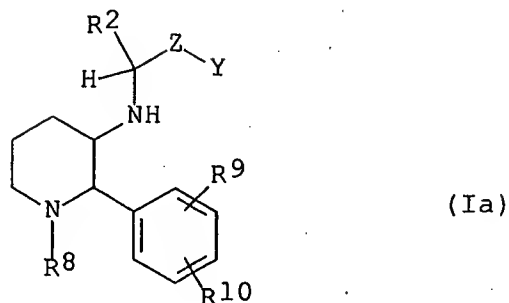


wherein R⁸, R⁹ and R¹⁰ are each as defined in claim 1, or its reactive derivative at the amino group or a salt thereof, with a compound of the formula (III):



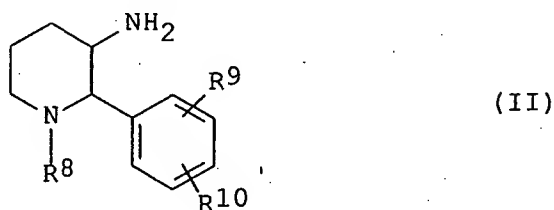
35 wherein Y, Z and R² are each as defined in claim 1,

or a salt thereof to give a compound of the formula
(Ia):



10 wherein Y, Z, R², R⁸, R⁹ and R¹⁰ are each as defined in
claim 1,
or a salt thereof, or

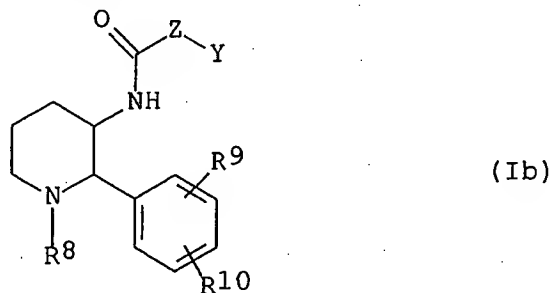
(2) reacting a compound of the formula (II):



20 wherein R⁸, R⁹ and R¹⁰ are each as defined in claim 1,
or its reactive derivative at the amino group or a salt
thereof, with a compound of the formula (IV):



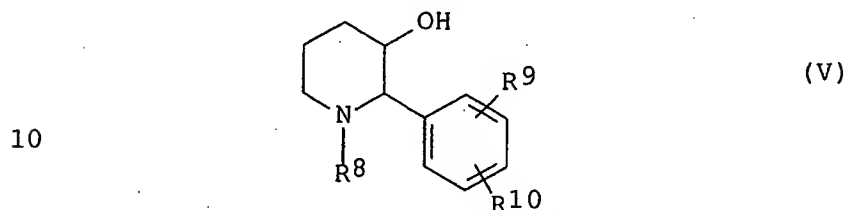
wherein Y and Z are as defined in claim 1,
or a salt thereof to give a compound of the formula
(Ib):



wherein Y, Z, R⁸, R⁹ and R¹⁰ are each as defined in
claim 1,
or a salt thereof, or

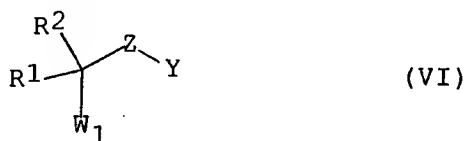
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(3) reacting a compound of the formula (V):



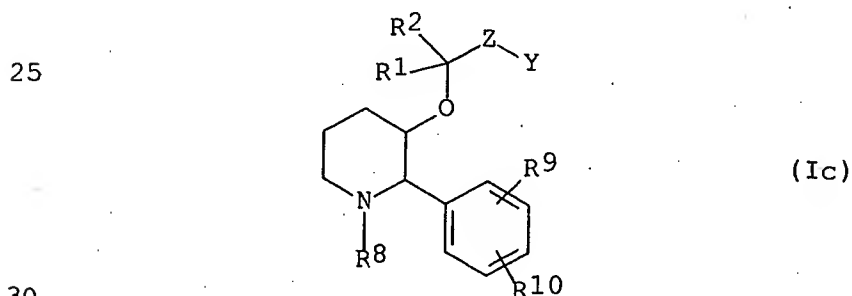
wherein R⁸, R⁹ and R¹⁰ are each as defined in claim 1,
or its reactive derivative at the amino group or a salt
thereof, with a compound of the formula (VI):

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wherein Y and Z are as defined in claim 1, and
W₁ is a leaving group,
to give a compound of the formula (Ic):

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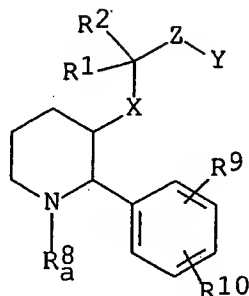


wherein Y, Z, R¹, R², R⁸, R⁹ and R¹⁰ are each as
defined in claim 1,
or a salt thereof, and

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- (4) eliminating the amino protective group of the compound (Id):

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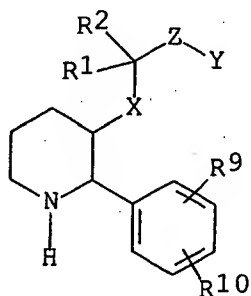
(Id)

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wherein X, Y, Z, R¹, R², R⁹ and R¹⁰ are each as defined in claim 1,

or a salt thereof to give a compound of the formula (Ie):

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(Ie)

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wherein X, Y, Z, R¹, R², R⁹ and R¹⁰ are each as defined in claim 1,

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or a salt thereof:

6. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.
7. A compound of claim 1 for use as a medicament.
8. A method for treating or preventing Tachykinin-mediated

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diseases which comprises administering an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof to human being or animals.

5 9. A compound of claim 1 for use as Tachykinin antagonist.

10. Use of a compound of claim 1 for manufacture of a medicament for treating or preventing Tachykinin-mediated diseases.

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